Critiques
of EPA External Review Draft
600/6-90/006A,
May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

prepared by

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Preface

On November 11, 1990, the R.J. Reynolds Tobacco Company (RJR) commissioned Biomedical and Environmental Consultants, Inc. (BEC) to independently review the EPA External Review Draft 600/6-90/006A, May 1990, titled "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children." Seven BEC members and three non-BEC scientists/clinicians undertook this task. A workshop was held on January 12/13, 1991, in Seattle at which the individual critiques were presented and discussed. These critiques, in alphabetical order of their authors, and an executive summary are presented in this report. The individual critiques reflect the different professional backgrounds and experiences of the authors but show consensus that the EPA Draft needs to be thoroughly revised.

The paramount issue in the EPA Draft is the question whether or not there is an association between environmental tobacco smoke (ETS) and lung cancer in adults. The second part of the EPA Draft deals with ETS effects on respiratory disorders. This topic is included in individual critiques of this report but not in the executive summary which focuses exclusively on the primary issue of ETS and lung cancer.

The Appendix to this report was prepared by Dr. Alan J. Gross, and Mr. Derek Janszen, following the workshop in Seattle.

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EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) document EPA/600/6-90/006A on "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children" is a preliminary external review draft, hereafter referred to as Draft, issued in May 1990.

Based on the review of data presented in the U.S. Surgeon General's report of 1986 on environmental tobacco smoke (ETS), the National Research Council (NRC) report of 1986 on the same subject, and on subsequently published studies, the Draft concludes that ETS is a Group A carcinogen. EPA's Risk Assessment Guidelines of 1986 define a Group A carcinogen as a human carcinogen, *a designation used according to EPA's 1986 Guidelines "only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer."*

According to the guidelines, "Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

The Draft based the Group A classification of ETS mainly on the results of statistical analysis of (1) 19 case-control studies and (2) two cohort studies. The critiques in this report examine the validity of the data and of the arguments upon which EPA's conclusion is based.

It should be realized that the Draft is not a scientific document containing new evidence, but a selective summary and a selective analysis of previously published data. It needs to be evaluated whether the original data were adequate or inadequate, accurate or inaccurate, and whether the authors of the Draft were justified or not justified, accurate or inaccurate, in their analysis and interpretation of data from others.

Meta Analysis

The Draft combines results of several previous studies in a statistical *meta analysis.* Meta analysis describes quantitative methods for combining results across a number of studies. The underlying tenet of this relatively new and not yet completely evaluated technique is that by combining results from a *representative* sample of a multitude of *comparable* studies a more accurate picture of reality may be obtained. Meta analysis can be applied to increase statistical power by analyzing total evidence from all studies simultaneously, and as a means of deriving an overall average risk estimate from the separate risk estimates of the individual studies. This statistical tool is useful, for example, when any effect that might exist is likely to be only moderate and when there is an expectation that, while effects of different studies may have different magnitudes, all of them may be expected to point in the same direction.

Strict criteria have been developed for the appropriate application of meta analysis (see, for example, Yusuf et al, 1985; Chalmers et al, 1989). these include (1) preparation of a detailed protocol, defining procedures and criteria to be used, *before* statistical analysis, (2) extensive data search to ensure that the studies pooled are representative of *all* existing studies, including those showing no effect, (3) comparability of what is measured and compared in the pooled studies, and (4) relative invariance of results when available data are reorganized or other relevant data added. As shown in the individual critiques of this report, none of these criteria are met in the Draft.

The 19 Case-Control Studies

Much of EPA's case against ETS rests on the results of EPA's meta analysis of 19 case-control studies with nonsmoking females exposed to ETS from smoking spouses. Closer examination shows that these studies vary widely in quality as well as in their definitions of exposure and endpoint, thereby violating one of the fundamental rules for the appropriate application of meta analysis. The Draft recognizes numerous confounding differences in the case-control studies but nevertheless subjects the data to meta analysis. These differences include (1) definition of ETS exposures, (2) inclusion of former smokers as nonsmokers, if they did not smoke for some minimum period, in some studies but not in others, (3) questions, leading to classification as ETS-exposed subjects, varied across studies, (4) exposure percentages vary from 15 to 84% across studies, (5) reference populations are defined by different parameters, (6) study design,

(7) experimental protocol, (8) data analysis and interpretation, (9) potential confounding factors, and last but not least (10) confirmation of primary lung cancers. Sterling et al (see critique by Sterling et al) counted at least eight different definitions of cases and twelve different definitions of exposure!

Various biases (e.g. , publication bias; selection bias; biases due to smoker misclassification, misdiagnosis of lung cancer, and proxy respondents) can and do lead to distorted and invalid results, as the following examples will show. The combined 19 case-control studies in the Draft yield a pooled risk ratio (RR) of 1.42 (95% CI 1.24, 1.62) following EPA's meta analysis. However, if the Varela study—a well conducted investigation showing *no* spousal ETS effects, that was omitted for no valid reasons—had been included in EPA's analysis, the RR would have been markedly reduced, namely to 1.27 (95% CI 1.13, 1.42). In addition, EPA elected to restrict its analysis to nonsmoking wives of smoking husbands, excluding nonsmoking husbands of smoking wives. The reason given in the Draft for the exclusion of ETS-exposed males is lack of data for the latter situation. However, such data do exist, albeit on a smaller scale. When subjected to similar analysis, the data for males show *no* increased risk of lung cancer for ETS-exposed males married to smoking females (RR=1.07, 95% CI 0.86, 1.33; see critique by Sterling et al in this report). Furthermore, the Draft lumps together studies based on U.S. and non-U.S. populations. However, for many cultural, social, economic, and genetic reasons, it is open to question whether the U.S. and non-U.S. populations can be combined. Estimation of risk for the U.S. population ought to be based on studies using the U.S. population as subjects. However, when this is done, the risk for females fails to be significantly elevated (RR=1.11, 95% CI 0.96, 1.28) which is also true for risk for males. (Risk for males is RR=1.05 95% CI 0.83, 1.31; see critique by Sterling et al in this report). The selection of those studies to be pooled that result in significantly elevated risk and the omission of the pool of studies that fail to support elevated risk is a serious flaw in the Draft's analysis. At the very least the Draft ought to have listed results from applying meta analysis to males and to U.S. and non-U.S studies separately. As is, the pattern of selection and omissions appears to betray a strong bias by the Draft's authors. The individual critiques in this report will highlight additional biases.

In addition to inappropriate use of statistical procedures and biases, the Draft contains a number of other flaws. For example, in attempting an ETS risk assessment for the national nonsmoking population, the Draft extrapolates from the (already questionable) spousal data to the general

population. Given the close physical proximity in a spousal relationship, this procedure appears inappropriate, introducing a positive bias because non-spousal ETS exposures generally tend to be to markedly lower concentrations than spousal ETS exposures.

The definition of lung cancer cases varies considerably across the case-control studies (e.g., see critique by Sterling et al, p 8-13/14).

Indoor air contamination with radon decay products, present at widely differing concentrations in indoor environment, is a confounding variable that is strongly implicated as a causal factor in the development of respiratory tract cancer. The Draft does not address this problem.

Detection bias, one of the major biases to be expected in observational cohort and case-control studies, is also ignored as a confounding variable: many lung cancers are not identified during life and spouses of smokers may be more likely than spouses of nonsmokers to seek and receive the tests and examinations that lead to a diagnosis during life.

The Cohort Studies

The Draft cites the results of cohort studies as additional evidence for the carcinogenic effect of ETS. At issue are the Hirayama study in Japan and the Garfinkel study in America. Hirayama used 265,118 subjects, Garfinkel used more than 1 million. Both studies were subject to criticism, the former more so than the latter which is generally regarded the technically better study. The Hirayama study has results that vary with the type of analysis designed to correct a number of basic flaws, most of them concerned with adequate age adjustment. For some of these corrections, the Hirayama study still shows a statistically significantly elevated lung cancer risk for nonsmoking wives exposed to ETS where there are smoking husbands, but for others it does not. The Garfinkel study never showed such a risk. Yet, the Draft authors chose to emphasize the Hirayama findings and to downplay the Garfinkel results. They proceeded with a quantitative ETS risk assessment for the nonsmoking US population, based on the combined results (Hirayama + Garfinkel), claiming a significant ETS risk. This procedure violates basic principles of epidemiological statistics: a valid quantitative ETS risk assessment for the US population must be based on US conditions and US data. The obvious reasons for this postulate are to exclude a host of confounding variables each of which can affect the results of such a study. These variables

include cultural, dietary, geographic, genetic and many other potential differences (e.g., average room size, interior arrangements, air changes per hour, composition of Japanese cigarettes) between American and Japanese populations. Such differences can affect the respiratory tract dosimetry of ETS significantly and preclude the uncritical transfer of the Japanese data to the U.S. population for quantitative risk assessment as opposed to qualitative risk assessment (see critique by Oberdörster). An ETS risk assessment for the nonsmoking US population, based on the Garfinkel data, shows *no* significant lung cancer risk and no dose-response relationship. Yet, the presentation and interpretation of the results of these two studies are rather biased in favor of the Japanese study (for further details see individual critiques). For example, the Draft states on page 3-43, "The Japanese cohort study alone provides *compelling* (editor's emphasis) evidence of a lung cancer risk associated with ETS exposure". Two sentences later, the Draft comments on the bigger, seemingly better and much more relevant Garfinkel study as follows: "Results of the American cohort study are *less conclusive*" (editors emphasis), instead of stating the simple fact that there was *no* evidence of such a risk in the American study.

The Draft authors appear quite unconcerned about the underlying possible causes for the puzzling discrepancy between the results of the two studies. Similar indifference to other discrepancies is evident elsewhere in the Draft. For example, there is a marked difference between relative lung cancer risk derived from epidemiology data and comparative dosimetric estimates from both particulate materials and vapor phase components, these dosimetric estimates being orders of magnitude lower (see, for example, critique by Stuart). It is scientifically unacceptable to choose among contradictory data those one likes and to disregard the others.

Additional Comments

The dosimetry of ETS is discussed in Appendix C of the Draft. Reference is made to an early International Commission on Radiological Protection (ICRP) particle deposition and retention model which, however, is described incorrectly in the text and in an accompanying figure. Appendix C shows a number of conceptual problems and, in many cases, evidence of inadequate grasp of the current state of the art of quantitative prediction of fractional deposition of inhaled particulates. Basic differences in relative deposition in tracheobronchial vs. peripheral lung regions between ETS and mainstream smoke (MS) exist, e.g., relative deposition per unit surface area is higher in the upper conducting airways for MS whereas for ETS it is higher in the transitional zone of the lower respiratory tract.

Furthermore, the authors of Appendix C appear to be unaware of the basic precepts of the rapidly developing science of physiologically based pharmacokinetic models, which describe dynamic and generally first-order interactive processes for distribution of agents from absorption site into blood and subsequently into target organs. Such models are particularly important for adsorption of substances like nicotine which is absorbed through mucosal sites of the mouth, and of the nasopharynx when inhaled in the gas phase (as in ETS), an important process which the draft document incorrectly states not to occur. (see critiques by Stuart, p. 9-7, and Bissell, pp. 2-3/4).

Assessment of Lung Cancer Risk

The Draft's assessment of lung cancer risk appears flawed for several reasons. To begin with, it is based on inappropriate statistical analysis (see Meta Analysis, above) that yields erroneous figures at the start. In addition, while the Draft acknowledges a number of confounding variables, other important confounding variables are ignored. Among them rank radon progeny (see critique by Stuart) and secondary exposure to occupational carcinogens in the home (see Appendix to critique by Sterling et al), to name just two. There appears to be no diligent effort in the Draft to search for potential alternative explanations for lung cancer among spouses of smokers. Of the variables acknowledged in the Draft, those whose adjustment tends to result in lower risk ratios, are played down as essentially inconsequential, supported by a selectively chosen literature reference (example: publication bias, p. 3-33).

Referring to the NRC report (1986), the Draft differentiates between "unexposed" and "truly unexposed" subjects. This differentiation is based on cotinine measurements in nonsmokers not knowingly exposed to ETS. These measurements were interpreted to indicate exposure to background ETS, based on the assumption that ETS is the only source of nicotine. Ignored is the fact that nicotine also occurs in certain vegetables of the *solanacae* family (e.g., egg plant, potatoes, green pepper, tomatoes) that might well account for at least part of the cotinine found in nonsmokers. Failure to recognize and adjust for this possibility casts doubt on the validity of the cotinine data as a measure of ETS exposure. Yet these questionable cotinine values are used in the Draft to convert "unexposed subjects" to "truly unexposed" subjects. The effect which adjustments have on RR is demonstrated in the following paragraph on page 3-32 of the Draft:

"the overall estimate of RR in the NRC report places the excess risk of lung cancer associated with spousal smoking at about 34%. An adjustment for possible misclassification of the never-smoker status reduced the value to 25%. A second adjustment to make this risk relative to a truly unexposed subject, i.e., to take into account a background level of exposure, raises the increased risk to 42%."

On page 4-28 of the Draft, it is further assumed that (1) lung cancer risk from passive smoking is linearly related to (these questionable) cotinine concentrations, (2) background ETS constitutes about one-third of the total ETS exposure of a nonsmoker married to a smoker, using (these questionable) cotinine concentrations as an index of total ETS exposures, and (3) cotinine is a constant multiple of the carcinogenic potency of ETS at low doses. The questionable validity of the cotinine data as indicators of ETS exposure renders all three assumptions questionable.

EPA's lung cancer risk assessment is based on linear extrapolation to zero of findings in smokers, who are exposed to *mainstream smoke* plus much higher concentrations of sidestream smoke than nonsmokers. This assumes that there is no threshold for ETS effects or, in other words, that even very low concentrations, such as typically encountered by nonsmokers in ETS, are harmful. It further assumes that mainstream smoke equals sidestream smoke. The latter assumption is demonstrably wrong, and the no-threshold assumption ignores effective defense mechanisms of the human body (e.g., macrophages, mucociliary clearance, enzyme induction/activation), capable of dealing with low concentrations of numerous insults. The no-threshold concept further ignores the phenomenon of hormesis (see critique by Wehner). While the EPA is policy-bound to adhere to the no-threshold concept, points that argue against this position should be discussed in the Draft.

Conclusions

The consensus of the authors of the individual critiques and participants in the Seattle workshop (January 12/13, 1991) can be summarized as follows:

(1) Attempting to determine biological effects of ETS is an extremely complex and difficult task vexed by numerous, often ill-defined confounding variables, insufficient measurements, lack of standardized experimental protocols, and controversial data interpretation.

(2) Because currently available data are incomplete and ambiguous, they cannot be used for a valid quantitative risk assessment for the general U.S. population.

(3) For reasons detailed in this report, EPA's classification of ETS as a Group A carcinogen is scientifically not justifiable: it does not meet the definition of a Group A carcinogen in EPS's 1986 Guidelines which requires "sufficient evidence from epidemiologic studies to support a *causal* (editor's emphasis) association between exposure to the agents and cancer.".

A.P. Wehner, Editor

A Critique of EPA External Review Draft 600/6-90/006A, May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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Meta Analysis

The method of analysis of multiple studies searching for the same end-point is well established in epidemiological usage (first suggested but not applied by Mantel-Haenzsel, 1959), and a MEDLINE search done by me lists over 200 recent applications of the method in the medical literature. It is important to understand that the method is not limited to, nor was it even originally designed for, studies in the social sciences, as suggested by the authors of the Industry critique. The authors of the EPA draft (hereinafter referred to as the "Draft") have undertaken reasonably appropriate analyses of the data they chose to analyze, even though this is a limited set and many criticisms can be leveled at the individual studies.

There has not been enough attention paid by the authors of the Draft to the inevitable shortcomings of the meta-analytic method. Because of the widespread use of meta analysis in modern epidemiological analysis of clinical trials, there has been extensive study of the strengths and limitations of the methodology. I draw, in particular, two studies to our attention. Chalmers et al (1989) very explicitly draw up a set of rules for selection of the studies that should be admitted to a meta-analytic retrospective study. Some of these rules certainly have not been met by the authors of the Draft under consideration. Laird and Mosteller (1990) review the statistical methodology in detail. The latter study is part of an issue of this referenced journal devoted to a review of the uses of meta analysis (in Int. J. of Technology Assessment in Health Care, vol 6, 1990).

Before losing track of an observation in a more detailed critique of meta analysis, it is important to note that there is a reasonably useful test of the strength of any particular meta analytic procedure. This test is the robustness or stability of the outcome of the analysis as more data sets are added.

Yusuf et al (1985) is the important source the Draft uses for much of its analysis about the design of meta analytic approaches, but they then proceed to ignore most of the important constraints suggested by Yusuf et al. I would like to consider one of the points made strongly by Yusuf et al. That is the question of "publication bias". This is clearly an important issue, but Yusuf tends to produce selfparalysis by the emphasis he places on this part of the process. Chalmers (1989), I believe, presents the more balanced view of the importance of a study selec-

tion and inclusion. He suggests an aggressive search of the relevant literature indices and sources, with attention to the possibility of unpublished studies. This author suggests, quite rightly, in my opinion, that the most important step in meta analysis is the development of a written protocol defining the selection criteria, specific exclusion criteria, the statistical tests to be used, the hypothesis to be tested and the methods that will be used for establishing the literature search for the data base. Both Chalmers and Laird suggest the possibility of a weighting scheme that could be defined *in advance* to weight various studies for their shortcomings or advantages.

The most important and well known difficulty of the meta analysis approach is mentioned almost in passing by the Draft authors, but I believe it needs much more attention than attributed to it. The shortcoming is that if there is a consistent bias present in all of the studies subjected to analysis that the meta analysis outcome will be equally biased, in fact Mantel concludes that in certain circumstances meta analysis can *amplify* bias. Gross (1989) has discussed a few of these biases, which include misclassification of disease, consistent misreporting of smoking status, socioeconomic class, weighting and others. Other biases that are present in the Draft's meta analysis include choices of cases and controls, second person interviews to determine smoking status and many others. The great difficulty is the existence of an unknown generally existing bias of design or experiment which causes similar outcome distortions in all of the studies meta analyzed. I cannot agree with either Gross (1989) or Layard (1989) that meta analysis is only appropriate if the study populations are homogeneous with respect to exposure indices, demographic, social and other classification parameters. As long as there has been no selection of studies by criteria upon which the outcome is dependent the method should be appropriate.

It is crucially important that the reader examining the outcome of the meta analysis knows the criteria for selection and inclusion in the study, since one should apply the analytic outcome only to the population groups preselected. This application is both inclusive and exclusive. That is to say, a meta analysis devised without regard to ethnic origin can only be used to make inferences about a similarly distributed set of studies of differing ethnic populations. It would also exclude the possibility of making a specialized inference about, for example, American caucasians.

The relative risk of passive smoking given in the NRC report, namely 1.3, has been criticized for preselection that did not meet these criteria (Letzel, H.E. et al, 1988). These authors concluded

that three of the studies included in the NRC (1986) report did not meet the preselection criteria established, and that these particular studies contributed greatly to the meta analysis test of significance. The same criticism can be made about the Draft, but in this case the selection criteria have not been shared with us, so we don't know the extent to which they have been violated. Also, the extent of data manipulation in the original studies used in the Draft's meta analysis is unacceptable, particularly when the nature of such manipulation has not been fully disclosed.

Koo(1988) reported another important confounding variable which may be generally present throughout most of the studies included in the Draft's meta analysis: the wives of nonsmoking husbands had generally healthier life styles and less exposure to other possible dietary and other sources of lung cancer. The authors are aware of the bias introduced by the self-reporting of smoking status of the "never-smoker". Surely few people today would report themselves as a smoker when they were indeed a never-smoker. All of the bias is in the other direction. In fact, in some cultures, the secret smoker female spouse may be very unwilling to share her smoking status with the interviewer. The Draft authors follow the lead of others in attempting to correct for this bias, but the results are simply not credible. Furthermore, their analysis is so sketchy that an independent review of the process is not easy. Letzel et al(1988) undertook the correction of smoker misclassification for the data of the NRC (1988) report and found that it created the necessity for "...accepting the null hypothesis or creating new empirical evidence and performing a really good study." I find Letzel et al's corrections of the data no more convincing than that of the EPA study.

I am sure it will be noted by all of our committee members that the use of "proxy responses" or "surrogate responses" to determine the smoker, nonsmoker classification is not consistent among the studies included in the Draft's meta analysis. The Draft authors suggest that the proxy approach is indeed reliable, but extensive review of the literature on the subject would not support such a position.

While considering the smoker misclassification issue I would draw your attention to the report by Friedman et al (1983) which raises an even more important issue about smoker classification for Americans in passive smoking studies. This report states that for 47% of nonsmoking wives married to smokers, there is no exposure to passive smoke in the home. This represents a strong

statement about social norms in the U.S.A. It would suggest strong spousal pressure for the smoker not to smoke while at home.

I will not take the time to review the data having to do with socioeconomic status of spousal non-smokers, since one of our Committee members has been involved in such studies and will undoubtedly report upon them in detail. Sufficient to say that it is clear that the likelihood of spousal exposure will be certainly greater in the blue-collar community. With such a socioeconomic bias, it is clear that other aspects of life style such as work environment exposure and nutrition will play major biasing roles in studies which fail to control for this variable.

Inferences from the Meta Analysis

For the S statistic analysis the authors of the Draft have chosen to use a "one-tail" test of significance for accepting or rejecting the null hypothesis that there is no higher risk ratio for lung cancer in those exposed to ETS than those who are not. One might argue with this approach, but it is a criterion often used in epidemiological studies. For example, the one-tail approach is frequently used in low risk ratio studies of cancer produced as the result of exposure to environmental radiations of one sort or another. Malcolm Pike has, for example, used a one-tail test for the significance of an increased odds ratio for leukemia in inhabitants of Utah exposed to the Nevada test site fallout (report in press).

Moreover, I believe that the extrapolations made in the Draft from spousal smoking to the national population are well beyond the range of credibility.

Nearly all of the studies included in the meta analysis are based upon exposure of a female spouse to sidestream smoke from a smoking husband. Even under the best of circumstances, which are not to be seen in this case, extrapolation to a national population, both male and female, will be an extremely uncertain process. In those cases where smoking in the home occurs, there is a special case of spousal propinquity which would maximize the nonsmoker's exposure to sidestream smoke. Smoking at the dinner table, in the car, in bed, at the television, will all be associated with nearness of the nonsmoking spouse. It has been suggested by several authors, and it seems a reasonable conclusion, that at the work place and outside the home the nonsmoker will tend to avoid the smoker, and even place restraints upon the smoker. The propin-

quity issue and the avoidance issue make, as far as I am concerned, extrapolation of spousal exposure data nearly useless for quantitative estimates of associated lung cancer deaths.

The spousal misclassification issue (as to smoker-nonsmoker) is treated in such a cavalier fashion in the Draft that it is hard to believe that the authors really examined the extensive review of the subject in the NRC (1986) report. I commend Table 12-5 from the NRC report for your consideration. This table does a model calculation assuming the real RR to be 1.0 and a misclassification among 100 000 women, of whom 35% are smokers, and 8% of these smokers misreport themselves as nonsmokers. The observed RR is 1.3 while the real RR is still 1.0. The likelihood becomes even greater that misreporting is a real bias when proxy reporting of smoking status is allowed. See also Lehnert et al (1984).

The Draft authors have proposed a model for correction of mostly female exposure data for extrapolation to men, but again their approach is not at all convincing.

The Cohort Studies

Two cohort studies from the literature, that of Hirayama (1984) and the study of Garfinkel (1985) are considered in the Draft. A third cohort study, that of Gillis et al (1984) is not considered and has generally received little attention from the research community even though it reports an RR of 3.0 for males and 1.00 for females. Of course the reason for ignoring the Gillis study is the small sample size, six females or four males in the exposed groups. The Hirayama study has received such wide-spread criticism that it is not necessary to dwell at length on the shortcomings of the study. Layard (1989) lists some of these as bias in the selection of the study sample, misclassification of lung cancer diagnosis, misclassification of nonsmoking status and inappropriate statistical analysis of the data. In spite of the extensive criticism of the Hirayama study, the Draft authors dwell extensively on its results. They principally make a point that there appears to be a dose-effect relationship, RR 1.42 for passive exposure to <14 cigarettes per day, RR =1.58 for 15-19 cigarettes per day, and RR 1.91 for passive exposure to >20 cigarettes per day. They do, however, use Garfinkel's data rather extensively. Since Garfinkel refused to assign statistical significance to the determined risk ratio of 1.17 (c.i. 0.93-1.47) as being different from 1.0, then further consideration of the data is quite inappropriate. The Draft authors rather queerly report that although a risk ratio of 1.0 is within Garfinkel's confidence limit that risk

ratios as high as 1.25 to 1.5 are also in the range. They neglect to point out that risk ratios a good deal less than 1.0 are also in the confidence limit. It is also disturbing to see them report on page 3-43 that "....the American cohort study weakly indicates an increased cancer risk....." when the author himself is much more circumspect.

It is surprising to me to see the following in the Draft.

"The American cohort study appears to contain more statistical uncertainty than the Japanese study. Some of the general factors contributing to uncertainty in study data are related to sample size, variability in the population sampled, sample design and protocol, treatment of missing or incomplete data, accuracy and reliability of collecting and reporting data, and methods of statistical analysis."

All of these purported shortcomings of the Garfinkel cohort study have been variously ascribed to the Hariyama study.

Dose-Effect Relationships

To establish a dose-effect relationship is the "Holy Grail" of studies of environmental carcinogens,. and in the Draft there has been an attempt to examine these relationships in the case-control studies included in their analysis.

Figure 3.4 shows a graphic representation of the dose-response data which the Draft lists in Table 3-7. With only one possible, but questionable exception, (LAMT) there is no statistical significance attributable to the dose-effect relationship. Interestingly, the Draft authors describe those studies (such as KOO, HUMB, LAMT and LEE) in which there is no relationship or an inverse relationship as "variable".

In the Draft a great deal is made of the dose-response relationship in the Hirayama (1984a) cohort study. In a further report on the Hirayama data (1984b), there are data that can be analyzed to show that the dose-response relationship issue is somewhat clouded if the age of the nonsmoking spouse was stratified with respect to age at the time of entry into the study. The dose-response relationship got weaker and weaker as the age at time of entry increased.

Dose-Effect Modeling

The Draft authors consider "cigarette equivalent" dose-response relationship as a possible approach to estimating the risk from environmental tobacco smoke (ETS) in Chapter 4 and in Appendix D. They agree that there are significant limitations on the use of the "cigarette equivalent" approach. The most important of these is that there is no useful way to make a comparison between exposure of the mainstream smoker and the individual passively exposed to sidestream smoke. It is interesting that after this insightful introduction to the problem, they state: " Legitimate reservations not withstanding, virtually all analytic approaches bear some assumptions and weaknesses, and most contribute something to our understanding."

Repace and Lowrey (1985) start with the affirmed fact that there is an established risk ratio for non-smokers. The model uses a probability weighted average for exposure to respirable suspended particulates (RSP) and a complicated model of space air change and number of burning cigarettes per unit volume of air space. The model predicts that exposure of U.S. nonsmokers ranges from zero to 14+ mg/day with an "86% exposure probability". The latter qualification indicates that 14% of adults are completely nonexposed. Their assumption that an average smoker consumes two cigarettes per hour is probably high, but there are more serious concerns than that. Repace and Lowrey base their estimate of lung cancer deaths on the Seventh Day Adventist (SDA) data of Phillips et al (1980a, 1980b). Based on the SDA data, Repace and Lowrey calculate that ETS caused 4700 lung cancer deaths among the 62.4 million nonsmokers over 35 years of age in 1980.

Based on the assumption of a linear dose-response relationship, Repace and Lowrey calculated that the ETS dose-response relationship was 5 lung cancer deaths per 100,000 per 1 mg tar per day.

There are serious reservations both about the SDA study itself, as used by Repace and Lowrey (Gross, 1989), but there are other fundamental flaws in the model. The first and most important is the assumption that there is a demonstrable RR for ETS exposure. Their independent estimate, based on a single-hit model and extrapolating from the RR for mainstream smoke, gives a dose-response estimate of 0.6 lung cancer deaths per 100,000 per 1 mg tar per day. These authors suggest that the rate determined from the SDA model is the more reliable, for reasons that are not apparent.

There are several other dose-effect (cigarette equivalent models) models which can be mentioned, but none are less subject to criticism than the Repace and Lowrey calculations. I mention Wells (1988), Robins et al (1986 NRC report appendix) and Vutuc (1984).

The Draft authors mention the Moolgavkar et al (1989) model as a possible approach but it is not extensively developed by them. This model is a two-stage model which includes growth kinetics of first-stage transformed cells. The model provides a reasonably good fit to the British Doctor data. The low-dose portion of the Moolgavkar curve from "doses" of 5 cigarettes a day down to 1 cigarette per day is described by a relationship where the relative risk is equal to 1 + 0.3d, where d is the number of cigarettes per day and the exposure is taken to be from age 22.5 years to present age 60 years. If one accepts the downward extrapolation of the British Doctor data to regions well below that at which data exist, the formula just expressed predicts a relative risk of 1.3 for exposure to one cigarette per day. The important caveat for this extrapolation is that one is extrapolating active smoking data and making application to a passive smoker. What is the passive equivalent of actively smoking one cigarette per day? McAughey et al (1989) found, with a radioactive tracer method, that for volunteers exposed continuously to sidestream smoke from two cigarettes, the tracheobronchial deposition of particulates was equivalent to 0.006 cigarettes per day. The Moolgavkar model would then predict a risk ratio of 1.002. From the NRC publication, dosimetry measurements were reported to lead to an estimate of 0.0001 to 0.005 cigarettes per day. The upper limit from these numbers would be essentially the same as from McAughey's study.

In considering the overall criticisms of the "cigarette equivalent" models one can do little better than quote Kilpatrick's rebuttal of the Repace and Lowrey paper (Kilpatrick, 1986). He points out that the one-hit model of these authors has a zero intercept term, implying that ETS is the sole cause of lung cancer in nonsmokers. He also points out that Repace and Lowrey assume perfect mixing of smokers and nonsmokers. That is to say, nonsmokers will not avoid smokers and vice versa. Furthermore, a general criticism of all of these models is that the ambient measurements may have little or no bearing on the amounts that actually reach the target tissue (Doll, 1985).

Wells, in his modeling, is subject to many of the criticisms levelled at Repace and Lowery, but in addition he assumes marriage to a smoker is synonymous with exposure to ETS, which we know

not to be the case for American spouses in particular. Furthermore, Wells combined morbidity and mortality and combines adjusted and unadjusted risk estimates without any discussion of the methods of adjustment when used. For females all cancers are included. For males only lung cancer is counted. All of these faults leave little to consider of value in the Wells report.

Biological Indicators of Exposure

It is relatively easy to relegate all other markers of exposure to ETS other than nicotine and cotinine to the trash bin. Nicotine and cotinine are, however, nearly tobacco specific. One of the better recent discussions of these markers is given by Jarvis (1989). Other indicators such as thiocyanate, carbon monoxide and polycyclic aromatic hydrocarbons are simply not specific enough or sensitive enough to be useful as indicators of exposure to ETS. The one exception is that there are dietary sources of nicotine that can confound measurements. Members of the family *solanacae,* such as potatoes, bell peppers, egg plant and others do contain nicotine, and their intake can seriously distort measurements of nicotine and cotinine in body fluids (Castro and Monji, 1986). In most cases, with reasonable care, the influence of dietary intake of these sources can be controlled. Without careful attention to dietary intake serious misinterpretation of data based on cotinine levels has been shown to be possible (Idle, 1990)

Nicotine has a half-life of only 1-2 hours in blood, so that measurements of this alkaloid are only useful for a brief period after exposure. Cotinine has a half-life of 10-20 hours in blood, so it is more useful for long term exposure.

For a number of very significant reasons cotinine levels in body fluids must be considered to be no more than qualitative, or, at best, semiquantitative measures of exposure to ETS. It has been well established that the distribution of nicotine in mainstream smoke is quite different from that in sidestream smoke. In the former, nicotine is associated with the particulate fraction, while in the latter nicotine is in the volatile phase (Tang et al, 1988). One could not then, conceivably, try to relate the biological level of cotinine in the nonsmoker with the number of cigarettes smoked in his presence, unless extensive correlative experiments were done to establish a useful association of measurements. The most important general limitation with the use of cotinine measurements is that it cannot be used as a surrogate for constituents of ETS other than nicotine without careful study and correlation. The measurements cannot be validly used to estimate

"cigarette equivalents" for risk estimation. Such an estimate, though, has indeed been made by Russel et al (1986).

Sepkopvic et al(1986) reported on the rate of cotinine and nicotine metabolism in both smokers and nonsmokers. This paper states that the rate of nicotine and cotinine metabolism in smokers and in nonsmokers is greatly different. If this were not the case it would be very surprising because the detoxification of most chemicals that do not normally exist in the body occurs via inducible enzyme systems, the activity level of which is controlled by the level of exposure. This fact alone rules out the determination of cotinine in body fluids as a reliable marker for exposure to ETS.

There is no methodological barrier to the use of cotinine concentrations as an indicator of ETS exposure. The concentrations are well within the present technology, but because they are so low, careful methodology and intercomparisons among laboratories are essential. Interfering substances exist and must be controlled for

Respiratory Disease and Respiratory Function in Children and ETS

Section 5 of the Draft deals with the relationship between ETS and respiratory disorders in children. This chapter is, in my opinion, the most superficially written and poorly interpreted part of what is, overall, already a disgracefully nonscientific document.

The key document for these effects is the 1986 NRC report on ETS, which draws conclusions that can be roughly paraphrased as follows:

1. Parental smoking, particularly by the mother, increases the risk of respiratory symptoms and illness in young children.

2. Parental smoking *may* be associated with small decreases in pulmonary function and *may* impair pulmonary development in small children.

Outside of the Draft there is another good review of the literature by Witorsch (1989) and Witorsch and Witorsch (1989) I particularly commend to you the extensive bibliography.

Also in a relatively recent review (also cited in the Draft), Rubin and Darmus (1988) tentatively concluded that there might be an association between parental smoking and respiratory disease in their children. They, however, rated each of 30 studies on the basis of seven individual criteria of study quality, including among others, data collection, estimates of smoke exposure, pathological criteria, etc. The authors found serious flaws of design and conduct in nearly all of the studies.

The Witorschs are swayed that there is some substance in the possibility that there is indeed an effect on pulmonary disease in children under five years of age, but that for older children there is no such relationship. They point out, however, that all of the confounding variables that affect the outcome of epidemiological studies of lung cancer and ETS are just as present and just as important for lung disease in children studies. Of these, the ones to which they assign the highest significance are socioeconomic status and occupations of the parents. Harlap and Davis (1974) in a quite old study already reported that, while they found an association of parental smoking with increased respiratory illness in infants, there was also an association with increased incidence of hospitalization of infants due to injury and poisonings. Of course the latter cannot be attributed causally to ETS, and is more probably an indicator of socioeconomic status.

Witorsch and Witorsch are convinced that no case can be made for the effect of parental smoking on pulmonary function, even for children under five.

It has been noted by several authors and commented on in the discussion attached to Witorsch (1989) by Robert Brown, that one cannot deconfound the effects seen in the infant as the result of ETS on the child from the effects that were established *in utero* as the result of maternal smoking.

Expressing a personal opinion, it is strange to me that, even though the evidence for infant pulmonary disease and ETS is somewhat more convincing than the adult lung cancer association, that the EPA has done such a trivial job analyzing the data and coming to conclusions. Maybe adult lung cancer sells better.

Conclusions and Recommendations

I find the study seriously flawed as a basis for federal regulatory action. The Draft has selectively reviewed the literature in such a fashion that significant bias towards accepting the evidence for a risk ratio greater than 1.0 for the association of adult lung cancer and ETS is introduced.

The analysis of the effects of parental smoking on childhood lung disease and lung function again draws conclusions contrary to the statistical evidence and warps the data to fit the pattern that they seem to have chosen.

In the book Environmental Tobacco Smoke, Nathan Mantel makes a number of incisive comments that should be read in the original by the members of this committee. Firstly, he appropriately points out that none of the cohort studies are truly cohort studies in the same sense as the British Doctors Cohort. All of the presently discussed ETS cohort studies are "record linkage" studies, subject to the usual difficulties with this kind of study. He suggests that the wrong study cohort is being assembled in each of the present reports. He proposes a study cohort of nonsmoking wives who are then differentiated as being married to smokers or nonsmokers.

Finally, Mantel again (1987) suggests that epidemiology is "too blunt a tool" to distinguish a relative risk of less than 2. The evidence from the radiation literature is all in support of this view. To appear soon is a study of fallout radiation and leukemia in which the study population of case-control design was the whole Mormon population of Utah, and it was not possible to statistically confirm a relative risk of about 1.2.

References

Castro, A. and Monji, N. (1986) Dietary nicotine and its significance in studies on tobacco smoking. Biochem. Arch. 2, 91-97.

Chalmers. T.C., Hewett, P., Reitman, D. and Sacks, H.S. (1989) Selection and evaluation of empirical research in technology assessment. Int. J. of Technology Assessment in Health Care. 5, 521-536.

Doll, R. (1985) Occupational Cancer, A hazard for epidemiologists. Int. J. Epidemiol. 14, 22-31.

Friedman, G.D., Petitti, D,B. and Bawol, R.D. (1983) Prevalence and correlates of passive smoking. American J. of Public Health, 73, 401-405.

Garfinkel, L. (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. J. Nat. Cancer Institute, 6, 1061-1066.

Gross, A.J. (1989) Risk assessments relating to environmental tobacco smoke. in *Environmental Tobacco Smoke*, pp 293-302. D.J. Echibon and J.M.Wu,eds.Lexington Books, Lexington, Mass.

Harlap, S. and Davis, A.M. (1974) Infant admissions to hospital and maternal smoking. Lancet, 1(7857) 529-532.

Hirayama, T. (1984a) Cancer mortality in non-smoking women with smoking husbands based on large scale cohort study in Japan. Prevent. Medicine 13, 680-690.

Hirayama, T. (1984b) Lung cancer in Japan: Effects of nutrition and passive smoking. in *Lung Cancer, Causes and Prevention*, Mizwell and Correa, eds. Verlag-Chemie International, New York.

Idle, J.R. (1990) Titrating exposure to tobacco smoke using cotinine—A minefield of misunderstanding. J. Clin Epidemiol. 43, 313-317.

Jarvis, M.J. (1989) Application of biochemical intake markers to passive smoking measurement and risk estimation. Mutation Res. 222, 101-110.

Kilpatrick, S.J. (1986) Letter to the Editor. Environment Intern. 12, 29-31.

Koo, L.C. (1989) Environmental tobacco smoke and lung cancer: Is it smoke or the diet? in *Present and Future of Indoor Air Quality.* Bieva et al, eds. Excerpta Medica, Amsterdam.

Laird, N.M. and Mosteller, F. (1990) Some statistical methods for combining experimental results. Int. J. of Technology Assessment in Health Care. 6, 5-30.

Layard, M.W. (1989) Environmental tobacco smoke and cancer: The epidemiological evidence.in *Environmental Tobacco Smoke*, pp 100-115. D.J. Echibon and J.M.Wu,eds.Lexington Books, Lexington, Mass.

Lee, P.N. (1988) An alternative explanation for the increased risk of lung cancer in non-smokers married to smokers. in, *Indoor and Ambient Air Quality.* pp 149-158 eds, R. Perry and P.W. Kirk, Selper Ltd, London.

Lehnert, G., Garfinkel, L., Hirayama, T., Schmähl, D. Überla, K., Wynder, E.L., and Lee, P.(1984) Roundtable discussion. Prev. Med. 13, 730-746.

Letzel, H., Blumner, E. and Uberla (1988) Meta analysis on passive smoking and lung cancer: effects of study selection and misclassification of exposure. Environmental Technology Letters, 9, 491-400.

Mantel, N. (1987) Lung cancer and passive smoking. Brit. Med. J. 294 p 440.

Mantel, N., and Haenszel, W. (1959) Statistical analysis of data from retrospective studies of disease. J. Nat. Cancer Institute, 22, 719-748.

Repace, J.R. and Lowrey, A.H. (1985). A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Envir. Internat., 2, 3-22

Tang, H., Richards, G., Gunther, K. et al (1988) Determination of gas phase nicotine and 3-ethenylpyridine, and particulate phase nicotine in environmental tobacco smoke with the collection bed capillary gas chromatography system. J. High Resol. Chrom. Commun. 11, 775-782.

Vsutuc, C. (1984) Quantitative aspects of passive smoking and lung cancer. Prev. Med. 13, 698-704.

Wells, A.J. (1988) An estimate of adult mortality in the United States from Passive Smoking. Environment Internat. 14, 249-265.

Witorsch, R.J. (1989) Parental smoking and respiratory health and pulmonary function in children: A review of the literature and suggestions for future research. in *Environmental Tobacco Smoke*, pp 205-226. D.J. Echibon and J.M.Wu,eds.Lexington Books, Lexington, Mass.

Witorsch, R.J. and Witorsch, P. (1989) A critical analysis of the relationship between parental smoking and pulmonary performance in children. Das Öffentliche Gesundheitswesen. 51, 78-83.

Yusuf, S., Peto, S.R., Lewis, J., Collins, R., and Sleight, P. (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. J. of Progressive Cardiovascular Diseases. 27, 335-371.

A Critique of EPA External Review Draft 600/6-90/006A, May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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I. The Logic of the EPA Draft with Regard to Use of Cotinine Measurements.

The issue of the validity and applicability of body fluid assays of nicotine metabolites is fundamental to assessing the validity of the EPA Draft's conclusions. Its approach to the estimation of lung caner risk from passive smoking involves the following steps:

1. Estimating the percentage of the population exposed to environmental tobacco smoke (ETS) based on these measurements.
2. Combining the results of case-control and cohort studies to obtain a summary estimate of relative risk (RR) of developing lung cancer for nonsmoking spouses married to smokers.
3. Correcting the summary RR estimate for smoker misclassification based in part on evidence derived from cotinine measurements. (RRM)
4. Further correcting RRM for the effect of general background exposure to ETS based on cotinine measurements. (RRB)
5. Combining RRB with the estimate of the population exposed to ETS in (1.) to obtain an estimate of the population attributable risk (PAR) for lung cancer in never-smoking females exposed to ETS.

The final section of the EPA Draft deals with respiratory (and related) disorders in children attributable to ETS. In this section, all the estimates of exposure are based on cotinine measurements, as are two of the studies of relative risk for specific conditions.

The EPA Draft draws the following distinctions in its use of cotinine measurements:

p1-5: "Some mathematical modeling is required to adjust for expected bias from self-reported misclassification status and to account for ETS exposure from sources other than spousal smoking. The approach, however, does not rely on a mathematical model of dose-response or low dose extrapolation of observations obtained at extraordinarily high exposure levels".

p4-28: "There is an important distinction between the use of cotinine as a surrogate dose for ETS to estimate lung cancer risk from background exposure and its use in the cigarette-equivalents approach. In the latter, the contention centers around the assumption that cotinine (or anything else such as RSP) is an equivalent dose surrogate for both passive and active smoking, i.e., that equivalent uptake in passive and active smoking implies equivalent carcinogenic risk".

While the approach adopted in the EPA Draft may or may not require assumptions about equivalent effects of active and passive smoking or risk, it does depend on two other basic implicit assumptions, namely:

1. That the only cause of body fluid elevations of nicotine or cotinine in human subjects is tobacco smoke (environmental or mainstream).

In other words, that the biological markers, (clinical assays of nicotine/cotinine) are 100% sensitive and specific as indicators of ETS exposure and show no false positives or false negatives due to analytical interferences of any kind.

2. The background exposure to ETS causes lung cancer and is the only cause of this disease in the nonsmoking population studied; therefore correction of RR estimates for this background exposure, based on cotinine measurements, is required.

It is not immediately obvious, nor is it anywhere explained in the EPA Draft, exactly how this assumption differs in practical terms from "the assumption that cotinine (or anything else such as RSP) is an equivalent dose surrogate for both passive and active smoking".

II. Examination of Assumptions

A. Assays of Nicotine and Nicotine Metabolites.

Our understanding of nicotine metabolism in man is not complete. The elucidation of the full extent of these pathways depends upon the isolation and identification of all of the metabolites involved. No fewer than twelve such intermediates have been identified so far in the rat by

radiometric high performance liquid chromatography (HPLC), and at least eighteen have been postulated. (Kyerematen, et al, 1987).

Cotinine is one of these compounds, and has a longer half-life in body fluids than the parent compound. It was for many years thought to be the principal metabolite, but more recent work has shown this not to be the case. Nicotine is also converted to nornicotine and to nicotine oxides, and cotinine itself is not an end product, but is further converted to any one of at least four other compounds (Kyerematen, et al, 1987). One of these, known as "metabolite 5" (Parvainen and Barlow, 1988) and tentatively identified as trans-3-hydroxycotinine (Neurath, et al, 198) is actually the major nicotine metabolite in smokers (Neurath and Pein, 1987). This is important in the present context not only as an indication of one of the numerous sources of biological variability in the cotinine assay, but also because this compound shows a 30% cross-reaction with the polyclonal anticotinine antibody which is the basis of the ELISA assay for cotinine (Schepers and Walk, 1988). This enzyme system is not only subject to genetic variability but, more importantly, is known to be very markedly induceable by drugs and other ingested substances (e.g., phenobarbital, Rudell, et al, 1987). One of these drugs is nicotine itself, which causes increased microsomal clearance of drugs like theophylline (Matsunge, et al, 1989), as well as nicotine and cotinine (Sepkovic, et al, 1986).

Two other sources of false positives have major implications for the interpretation of cotinine assays as surrogates for ETS exposure.

The first of these is caffeine, which is an exogenous source of analytical interference since it co-elutes with cotinine on several different reversed-phase HPLC assays, causing spurious elevations (Thuan, et al, 1989). This problem occurs in assays performed by the methods of Machecek and Jiang, (1986), Hariharan, et al (1988), Watson (1977), Maskarinec, et al (1978), Kyerematen, et al, (1982) and Hortsmann (1985).

Even more fundamentally problematic, however, is the fact, evidenced by the efficacy of snuff and Nicorette chewing gum, that nicotine is quite efficiently assimilated orally (Russell, et al, 1980). This is because of the recent discovery that tobacco and tobacco smoke are not the only common environmental sources of elevations in body fluid nicotine/cotinine levels. Common dietary sources are now known to exist. A variety of foods, (potatoes, eggplants, green peppers,

green tea, and certain brands of instant tea) contain sufficiently high concentrations of dietary nicotine to cause significant false positive cotinine elevations and resulting misclassification of ETS exposure (Idle, 1990). It appears that the nicotine is endogenous to the plants, but an additional potential source is absorbed insecticide nicotine on vegetables from certain countries. This may potentially also be a source of dietary nornicotine and cotinine itself (Idle, 1990).

False positive elevations of cotinine assays by dietary nicotine provide an alternative explanation for certain problematic finding in the ETS exposure literature. (Matsukura, et al, 1984; Pettenger, 1985; Adlkofer, et al, 1985). It will likely necessitate a downward revision in the estimation of the percentage of the population exposed to ETS based on nicotine/cotinine assays, and in the estimation of the rate of misclassification of smoking status based on these assays.

B. Problems with Nicotine and Nicotine Metabolites as Surrogates of Potential ETS Carcinogen Exposure.

As stated earlier, it is hard to understand the rationale for the correction of relative risk for "background" ETS exposure without implicitly assuming the relationship that is supposed to be demonstrated, namely that ETS causes lung cancer. This is circular reasoning. The error is only compounded by performing this "background" correction based only on cotinine measurements and then attempting to deny that. (EPA Draft, p. 4-28). Cotinine measurements are, in fact, being used as dose surrogates in so doing.

To quote directly from the EPA Draft; p 4-15:

"A difficulty in assessing this approach lies in evaluating the assumption that apparent differences between passive and active smoking are negligible or have cross-effects that cancel. For example, MS and SS differ in the relative composition of carcinogens identified in tobacco smoke and in their physicochemical properties in general. The lung and systematic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS as it ages. Passive and active smoking also differ in characteristics of intake-intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation. To help illuminate relationships and identify parameters where additional information would be helpful on this topic, a mathematical model for comparison of dosimetry of passive and active smoking was constructed as a basis for further study (Appendix C).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, concludes 'the differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers'. A recent consensus report of an IARC panel of experts (Saracci, 1989, p.3) states that 'lacking knowledge of which substances are responsible for the well established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential'. The U.S. SG report devotes a three page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. SG, 1986). It concludes with 'these limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk complex and potentially meaningless process'."

III. Conclusions/Recommendations

The papers upon which the EPA Draft's estimates of population exposed to ETS, correction for smoker misclassification, and correction for background exposure to ETS are based, should be carefully re-examined. All of these papers which depend upon assays of nicotine metabolites in body fluids for their conclusions can be meaningfully used for these purposes only if careful dietary histories have been obtained. The analytical results must either have been or be capable of being corrected for the dietary sources o false positive analytical results to avoid a systematic bias toward overestimating ETS exposure in all cases.

References

1. Adlkofer, F. Scherer, G, Hees, U. Passive smoking. (1985). N. Eng. J. Med., 312, 719-720.
2. Hariharan, M. Vannoord, T, Greden, JF, (1988). An HPLC method for routine simultaneous determination of nicotine and cotinine in plasma. Clin. Chem., 34, 724-729.
3. Hortsmann, M. (1985). Simple HPLC method for rapid determination of nicotine and cotinine in urine. J. Chromatog., 344, 391-396.

4. Idle, JR, (1990). Titrating exposure to tobacco smoke using cotinine–a minefield of misunderstandings, J. Clin. Epidemiol., 43, 313-317.

5. Kyerematen, G A, Damiano, M D, Dworchik, B H, Vesell, E S, (1982). Smoking-induced changes in nicotine deposition: application of new HPLC assay for nicotine and its metabolites. Clin. Pharmacol. Ther. 32, 379-382.

6. Kyerematen, G A, Taylor, L H, de Bethizy, J D, Vesell, E S, (1987). Radiometric HPLC assay for nicotine and twelve of its metabolites. J. Chromatog. 419, 191-203.

7. Machecek, D A, Jiang, N S, (1986). Quantification of cotinine in plasma and saliva by liquid chromatography. Clin. Chem. 32, 379-382.

8. Maskarinec, M P, Harvey, R W, Caton, J E, (1978). A novel method for the isolation and quantification analysis of nicotine. J. Anal. Toxicol., 2, 124-126.

9. Matsakura, S, Tomhiku, T, Norikazu, E, et al, (1984). Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers N. Eng. J. Med., 311. 828-832.

10. Matsunga, S K, Plezia, P M, Karol, M D, Katz, M.D. Camilli, A E, Benowitz, N L, (1989). Effects of passive smoking on theophylline clearance. Clin. Pharmacol. Ther., 46, 399-407.

11. Nakayama, H, Fujihara, S, Nakashima, T, Kurogochi, Y, (1987). Formation of two major nicotine metabolites in livers of guinea pigs. Biochem. Pharmacol., 36, 4313-4317.

12. Neurath, G B, Dunger, M. Krenz, O, Orth, D, Pein, F G, (1988). Trans-3'-hydroxycotinine–a main metabolite in smokers. Klin. Wochenschr., 66, (Suppl. 11), 2-4.

13. Neurath, G B, Pein F G, (1987). Gas chromatographic determination of trans-3'-hydroxycotinine, major metabolite of nicotine in smokers. J. Chromatog., 415, 400-406.

14. Parvainen, M T. Barlow, R D, (1988). Assessment of exposure to environmental tobacco smoke using an HPLC method for the simultaneous determination of nicotine and two of its metabolites in urine. J. Chromatog., 431, 216-221.

15. Pittenger, D J, (1985). Letter to the editor. N. Eng. J. Med., 312, 720.

16. Rudell, U, Foth, H, Kahl, G F, (1987). Eight-fold induction of nicotine elimination in perfussed rat liver by pretreatment with phenobarbital. Biochem. Biophys. Res. Comm., 148, 192-198.

17. Russell, M A H, Raw, M, Jarvis, M, (1980). Clinical use of nicotine chewing-gum. Brit. Med. J., 280, 1599-1602.

18. Schepers, G, Walk R-A, (1988). Cotinine determination of immunoassays may be influenced by other nicotine metabolites. Arch. Toxicol., 62, 395-397.

19. Sepkovic, D W, Haley, N J, Hoffmann, D, (1986). Elimination from the body of tobacco products by smokers and passive smokers. J. Am. Med. Assoc., 256, 863.

20. Thuan, NTL, Migueres, M L, Roche, D, Roussel, G, Mahuzier, G, Chretien, J, Ekindjian, O G, (1989). Elimination of caffeine interference in HPLC determination of urinary nicotine and cotinine. Clin. Chem., 35, 1456-1459.

21. Watson, I D, (1977). Rapid analysis of nicotine and cotinine in urine of smokers by isocratic high-performance liquid chromatography. J. Chromatog., 143, 203-206.

A Critique of EPA External Review Draft 600/6-90/006A, May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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Introduction

In the past decade, a number of epidemiologic studies have assessed the relationship between passive smoking and the incidence of lung cancer (1-17). Fewer studies have addressed the question of a possible relationship between environmental tobacco smoke (ETS) and respiratory infection in infants and children (see 18-20 as examples). The findings in the epidemiologic studies of ETS and lung cancer have ranged from no detectable increase in lung cancer risk (8,15) to a modest (less than two-fold) increase (2-5); however, many studies have reported increases which are of small magnitude and are statistically insignificant (1,6,7). In 1986, Wald et al. (16) performed a meta analysis of the data then available and concluded that there was a slightly increased risk of developing lung cancer associated with exposure to ETS. Recently, Janerich et al. (17) reported a case-control study of 191 lung cancer patients and concluded that only that group of nonsmokers who were exposed to ETS in childhood and adolescence had an increased risk of lung cancer (odds ratio = 2.07, 1.16-3.68).

The authors of the EPA Draft reviewed the published data with regard to ETS and lung cancer (excluding the Janerich report) and ETS and pulmonary infection. They concluded that ETS is responsible for a large number of lung cancer deaths among nonsmokers, as well as an increased incidence of pulmonary infection among infants and children.

Analysis of EPA Draft

The EPA Draft is not a scientific document; rather it is a selective summary and a selective analysis of data available in the literature. In essence, it is an interpretation or re-interpretation of the data of others. Consequently, it may be flawed either because the original data were inadequate or inaccurate, or because the authors of the Draft were inaccurate in their interpretation of the data of others.

The Draft relies heavily on a meta analysis of a series of epidemiologic studies of ETS and lung cancer risk. It dismisses as invalid the dosimetric approach to analysis which is called the "cigarette-equivalent" approach. Two reasons are given for this dismissal:

1) The metabolism of nicotine is different in smokers and nonsmokers.
2) The carcinogens are different in mainstream and sidestream smoke. The Draft

does not consider animal models. This is reasonable in view of the fact that there are no valid animal models of human lung cancer.

Epidemiologic Studies and Meta Analysis

After reviewing the Draft and listening to my colleagues, I have concluded that the interpretations and conclusions of the authors of the Draft are seriously flawed. The major defects to be found in the analysis and interpretation of the data in the literature are the following:

1. The effect of non-reporting of negative studies are mentioned but not really considered in the Draft (see pages 3-33); i.e. publication and reporting bias are acknowledged but not taken into account.
2. Only females are considered, and the statistically non-significant data for males are dismissed.
3. Confounding and possibly confounding factors which may invalidate the perceived association between ETS and lung cancer are not considered. These may include radon exposure, industrial (including diesel exhaust), exposure and perhaps other factors related to the socioeconomic status of the populations studied.
4. Incorrect diagnosis of lung cancer where this diagnosis was derived only from death certificates and not confirmed by independent and blinded histologic analysis.
5. Variability in the criteria for defining ETS exposure which should render invalid the pooling of data from several of the independent studies.
6. The failure to consider or explain the lack of a clear dose-response relationship between ETS and lung cancer incidence (see studies by Koo and Garfinkel as examples).
7. The misidentification of smoking status by questioning surrogates.
8. The use of cotinine as a measure of defining "truly nonsmokers," whereas it is dismissed as invalid for a cigarette equivalent analysis.
9. The effects of ETS exposure outside the home are not considered. This is part of the larger problem of defining the baseline for nonsmokers and of the extent of ETS exposure.
10. Studies acknowledged to be of poor quality (Hirayama et al.) are given emphasis, whereas good-quality studies (Garfinkel) are underemphasized.
11. Differences between Asian and American studies in the quantitative and qualitative aspects of ETS exposure are not considered.

12. The significance of a relative risk ratio of about 1.2 is not discussed in a critical and unbiased fashion.

Cigarette-Equivalent Approach

The details of this dosimetric approach are so well known that I shall not discuss them here but basically it has the following elements: 1) What is the dose-response curve for lung cancer incidence vs. numbers of cigarettes smoked per unit time for smokers? 2) Can the numbers of cigarettes per unit time be calculated for nonsmokers exposed to ETS? 3) Can one calculate a risk for nonsmokers based on this cigarette equivalent calculation?

This approach has certain requirements: 1) Dosimetry for smokers must be well defined even at low levels of exposure. 2) One must have a valid measurement which would allow one to calculate the exposure of nonsmokers. 3) The putative carcinogenic materials to which smokers and nonsmokers are exposed must be similar in biologic activity.

Let us examine each of these requirements and see whether a cigarette equivalent approach can be used to assess potential risks of ETS.

1. Dose-response curve for smokers.

This subject has been studied extensively for more than two decades and there is an abundant literature on the relationship between cigarette consumption in smokers and lung cancer incidence (see Moolgavkar et al. ref. 21 as a relatively recent summary).

2. The measurement of tobacco smoke exposure in nonsmokers.

Cotinine is the best biologic marker of exposure to the nicotine in tobacco smoke despite certain limitations: 1) Nicotine can be ingested with certain vegetables; and 2) The metabolism of nicotine/cotinine is different in smokers and nonsmokers. Both these limitations, if recognized and taken into account, will allow a reasonably accurate measurement of tobacco exposure in nonsmokers if the analytic study is properly constructed. Indeed, both factors will tend to result in an overestimation of the extent of ETS exposure in nonsmokers. Note that the EPA Draft sometimes uses this approach to define "truly nonsmokers."

3. Potential carcinogens in ETS.

The concentrations of a number of known carcinogenic compounds differ in mainstream smoke, sidestream smoke and in ETS. Furthermore, they may differ in ETS as a function of time and environmental factors. Nevertheless, the concentration of a number of carcinogenic compounds in mainstream smoke and ETS is known with precision for a variety of environments and is generally if not always of lower concentration in ETS than in mainstream smoke. While I do not have such data at my fingertips, I believe that such data are available.

In view of these considerations I believe that it is possible to determine a *maximal* value of cigarette exposure for nonsmokers, and that a cigarette-equivalent analysis is reasonable even if imperfect. Indeed, such an analysis would be considerably more precise than the crude tools available to the epidemiologist. My rough calculation is that a nonsmoker in a household where 20 cigarettes per day were smoked, would be exposed to the equivalent of less than one cigarette per day, i.e., a level which few people would argue is hazardous.

Summary and Conclusions

The EPA Draft is a weak document. It is seriously flawed in its analysis and interpretation of the epidemiologic studies of ETS and lung cancer. Although I have not discussed the details, the same defects can be found in the analysis of epidemiologic studies of ETS and respiratory infections in infants and children. The report appears to be biased in its conclusion although one cannot say whether this is an intentional bias or due to a lack of expertise on the part of the authors. I do not believe that there is sufficient evidence for classifying ETS as a known human carcinogen or even a "probable" carcinogen.

References

1. Garfinkel, L.: Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J. Nat. Can. Inst. 66: 1061-6, 1981.

2. Hirayama, T.: Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev. Med 13: 680-84, 1984.

3. Trichopoulos, D. et al: Lung cancer and passive smoking: conclusion of a Greek study. Lancet 2: 677-80, 1983.

4. Correa, P. et al: Passive smoking and lung cancer. Lancet 2: 595-7, 1983.

5. Garfinkel, L. et al: Involuntary smoking and lung cancer: a case-control study. J. Nat. Can. Inst. 75: 463-9, 1985.

6. Akiba, S. et al: Passive smoking and lung cancer among Japanese women. Cancer Res. 46: 4804-7, 1986.

7. Dalager, N.A. et al: The relation of passive smoking to lung cancer. ibid 46: 4808-11, 1986.

8. Kabat, G.C. and Wynder, E.L.: Lung cancer in nonsmokers. Cancer 53: 1214-21, 1984.

9. Sandler, D.P. et al: Cumulative effects of lifetime passive smoking on cancer risk. Lancet 1: 312-5, 1985.

10. Sandler, D.P. et al: Cancer risk in adulthood from early life exposure to parents' smoking. Am. J. Publ. Health, 75: 487-92, 1985

11. Sandler, D.P. et al: Passive smoking in adulthood and cancer risk. Am. J. Epidem. 121: 37-48, 1985.

12. Pershagen, G. et al: Passive smoking and lung cancer in Swedish women. ibid: 125: 17-24, 1987.

13. Koo, L.C. et al: Measurements of passive smoking and estimates of lung cancer risk among nonsmoking Chinese females. Int. J. Cancer 39: 162-9, 1987.

14. Humble, C.G. et al: Marriage to a smoker and lung cancer risk. Am. J. Publ. Health, 77: 598-602, 1987.

15. Chan, W.C.: Lung cancer in nonsmokers in Hong Kong. In: Grundmann et al (eds.), *Geographical Pathology in Cancer Epidemiology,* Fischer Verlag pp. 199-202, 1982.

16. Wald, N.J. et al: Does breathing other people's tobacco smoke cause lung cancer? Brit. Med. J. 293: 1217-23, 1986.

17. Janerich. D.T. et al: Lung cancer and exposure to tobacco smoke in the household. NEJM 323: 632-6, 1990.

18. Evans, D. et al: The impact of passive smoking on emergency room visits of urban children with asthma. Am. Rev. Res. Dis 135: 567-72, 1987.

19. Fergusson, D.M. et al: Parental smoking and lower respiratory illness in the first three years of life. Epidemiol. and Commun. Health 35: 180-4, 1981.

20. Ferris, B.G. et al: Effects of passive smoking on health of children. Environ. Health Perspect. 62: 289-95, 1985.

21. Moolgavkar, S.H. et al: Cigarette smoking and lung cancer: reanalysis of the British doctors data. J. Natl. Cancer Inst. 81: 415-20,1989.

A Critique of
EPA External Review Draft
600/6-90/006A,
May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

prepared by

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My comments refer to four main features of the EPA document. They are:

(1) its status as an editorial review of existing work rather then a presentation of new scientific evidence; (2) the acceptance, for statistical "meta-analysis", of data whose distortions and low scientific quality are ignored; (3) the absence of appropriate attention to problems of recall bias and detection bias; (4) the overt or subtle prejudice with which the authors have selected "evidence" for citation.

1. Editorial Review

The EPA Draft is not a "scientific document" containing new evidence. Instead, the Draft is an editorial review of existing evidence and of existing reviews. Accordingly, the EPA Draft cannot be appraised with any of the standards customarily applied to a "scientific report". As a review and set of editorial judgments, the EPA Draft must be evaluated for its attention to the scientific quality of the "news" from which the editorial review is derived, and for the quality and fairness with which the editorial is constructed.

2. Statistical Meta-Analyses

In contrast to previous editorial reviews (by the Surgeon General and the NRC), the EPA Draft also presents a statistical meta-analysis of the existing data. For this purpose, the "news" contained in existing epidemiologic studies has been accepted at its face value, and then subjected to various forms of statistical combination and calculation. The process of statistically combining and re-calculating published data was carried out without any attention to three sets of generally accepted criteria that have been established as conditions *sine qua non* for the scientific integrity of a meta-analysis. The three sets of criteria are as follows:

a. Formal protocol: To avoid the biases that can arise when investigators selectively choose the publications to be included, a careful, formal protocol must be established before the meta-analysis is done. The protocol should indicate the exact procedures to be used in searching the literature, in selecting the studies to be included in the analysis, and in deciding which ones will be excluded.

b. Precautions to avoid "publication bias": Because "publication bias" and the "file-drawer phenomenon" may lead to a substantial overemphasis on "positive results" in the published literature, the conductors of a meta-analysis should also institute a thorough search to find unpublished or otherwise unpublicized evidence of "negative" results. Without such a search, a meta-analysis based on published literature will inevitably be biased toward "positive" results when the data are pooled.

c. Randomized-trial evidence: To avoid the diverse problems of bias that can arise when cause-effect relationships are studied in the absence of randomized assignment of the compared agents, the evidence pooled in a meta-analysis should preferably come from randomized trials.

Although not everyone agrees about the scientific conclusions that can be drawn from a statistical meta-analysis, there is universal agreement that the foregoing three criteria should be fulfilled for the analysis to have scientific integrity and credibility. The EPA meta-analysis did not fulfill any of these three criteria. There was no formal protocol, no attention to publication bias, and, despite the fact that none of the included studies came from a randomized trial, no appropriate attention to the inevitable biases that must be considered and appropriately adjusted (if possible) when the basic information comes from non-randomized epidemiologic research.

3. Recall and Detection Bias

The EPA Draft gives inadequate attention to two of the major biases to be expected in observational cohort and case-control studies. One of them, recall bias about exposure to ETS, is generally dismissed by the EPA Draft authors as making odds ratios tend to the null value (i.e., 1). The authors ignore the high likelihood that for the cited clinical conditions, the patterns of recall bias will almost always go in the same direction, not in random cancellations. A separate problem, detection bias, is wholly ignored despite the fact that many lung cancers are not identified during life and that the spouses of smokers may be much more likely than spouses of non-smokers to seek and receive the tests and examinations that lead to a diagnosis during life.

4. Unfair Selection and Emphasis

In several locations and assertions, the authors of the EPA Draft display their own "editorial-review bias" in choosing the evidence they will emphasize. Perhaps the most obvious example of this "editorial-review bias" is in the emphasis given to the Hirayama cohort study, ignoring the Garfinkel cohort study. These are the only two pertinent cohort studies available to the Draft authors, but the Garfinkel study, which is generally regarded as having much better quality, found a negative result, (i.e., no statistically significant link between ETS and lung cancer), whereas the Hirayama study, which has been heavily criticized, was positive. In their conclusion, the authors focus only on the Hirayama study, ignoring the fact that when Hirayama made the necessary corrections to his data (in a subsequent publication), the result was much less positive. Thus, "editorial-review bias" has had a double impact. The EPA Draft authors emphasize the first Hirayama report, ignoring his subsequent correction; and they also ignore the contradictory Garfinkel report.

Another obvious example of "editorial-review bias" is the assertion on page 4-22 that ratios of 1.02 and 1.07 indicate excess risk. Because these ratios are so close to 1, I cannot think of a knowledgeable epidemiologist who would take them seriously.

Several other statements could be cited to document the bias of the EPA Draft writers. The only other one I shall note is their use of terms such as "showed" and "demonstrated" when the results of a particular study go in the desired direction (i.e. increased risk for passive smoking) and "not helpful" when the results go in the opposite direction.

A Critique of EPA External Review Draft 600/6-90/006A, May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

prepared by

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Introduction

This document was developed to supplement reports by theNational Research Council and the U.S. Surgeon General in assessing the health effects of exposure to environmental tobacco smoke (ETS). Both of those reports were published in 1986 and several more recent studies were deemed valuable in aiding the Environmental Protection Agency in making correct judgments as to possible carcinogenic effects of ETS, as well as respiratory disorders in children.

A meta analysis of results from diverse epidemiological studies was used to establish large numbers which would behelpful statistically in ascertaining the biological significance of ETS on human health.

Comments

The use of meta analysis to statistically analyze studies with such diverse testing methods and parameters for measurements tends to invalidate the statistical analysis. However, there are important findings associated with studies reported. One is the trend in relative risk associated with increased exposure to ETS. Obviously, identical environmental conditions to test effects on all smokers vs nonsmokers are needed to satisfy all critics, this because of other possible environmental contaminants.

Precise quantities of chemicals which subjects actually inhaled from environmental tobacco smoke are not well defined. Housing space, ventilation systems, humidity, and other variables may have led to apparent discrepancies between studies due to different exposure concentrations. There are some trends which are suggestive of passive smoking being associated with the etiology of cancer. However, more research and more coherent assessment of past research is required before ETS can be classified as a Group A carcinogen.

The discussion which follows is presented in an effort to try to identify possible reasons for seeming discrepancies observed in these ETS studies and to identify physiological reasons for respiratory disorders in children exposed to ETS. Phenolic compounds, nicotine, and other aromatic compounds liberated from burning tobaco are potentially toxic and/or pharmacological agents which affect many susceptible individuals. Such volatile chemicals in tobacco are impor-

tant in influencing the taste and aroma of tobacco smoke (1). One of the effects of these compounds is to evoke the release of catecholamines. This subsequently can initiate the synthesis and release of eicosanoids (prostaglandins, thromboxanes, and leukotrienes). These inflammatory agents may in turn cause asthma, irritation of nasal passages, headaches, cardiovascular disorders, inflamed intestines, inflamed lungs, etc. (2). Some individuals are much more susceptible to these chemical responses than others, and some seem to respond more to the compounds by inhalation than ingestion (and vice versa). Allergic and pharmacological effects are both involved. For example, Ronchetti et al. (3) compared 179 children in fourth grade from three Italian towns whose parents smoked with those who were nonsmokers. Those children whose parents smoked had higher IgE levels plus significantly higher total counts and percentages of eosinophils. Eosinophilic inflammation of the airways is correlated with the severity of asthma (4).

Another perspective of the impact of allergy related to tobacco smoke comes from the study of Murray and Morrison (5) in Canada. They examined 620 children, 1 to 17 years of age, who were nonsmokers but had a history of atopic dermatitis. Children with a history of atopic dermatitis were much more likely to have asthma if the mother was a smoker than if she was a nonsmoker (79% versus 52%; p=0.001). Similarly, if atopic dermatitis was found on examination, the percentages with asthma were 74% and 44%, respectively. By contrast, the children with no history of atopic dermatitis had asthma as frequently if the mother was a nonsmoker (42%) as when she was a smoker (40%).

References

1. Weeks, W.W., Chaplin, J.F., and Campbell, C.R. Capillary chromatography: Evaluation of volatiles from flue-cured tobacco varieties. J. Agric. Food Chem. *37:*1038, 1989.

2. Ninnemann, J.L. Prostaglandins, leukotrienes, and the immune response. Cambridge University Press, New York, 1988.

3. Ronchetti, R. et al. Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. J. Allergy Clin. Immunol. *86:*400, 1990.

4. Bousquet, J. et al. Eosinophilic inflammation in asthma. N Engl. J. Med. *323:*1033, 1990.

5. Murray, A.B., and Morrison, B.J. It is children with atopic dermatitis who develop asthma more frequently if the mother smokes. J. Allergy Clin. Immunol. *86:*732, 1990.

A Critique of EPA External Review Draft 600/6-90/006A, May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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Abstract

The issue of whether there is an association between exposure of nonsmokers to environmental tobacco smoke (ETS) and their prevalence of lung cancer is a pervasive one. In 1986, the National Research Council and the Surgeon General both published reports purporting to demonstrate such an association. These documents, unfortunately, were flawed on many scientific grounds and when adjustments were made where they could be, there proved to be a total lack of such an association. Now, four years later, the Environmental Protection Agency (EPA) issued a draft document dealing with this same issue. It becomes clear upon careful scrutiny of this Draft that many of the previous flaws in the study design remain uncorrected in the Draft. This is especially true in the case of an attempt to use, again, meta analysis to combine the results of 21 case-control studies, each of which addresses the question of whether individuals exposed to ETS at a higher level are more likely to develop lung cancer than those at a lower level. Unfortunately, this meta analysis does not account for the many biases that have existed and still exist in these studies and so reduces itself to becoming merely an "interesting statistical exercise" with no import.

Introduction

The preparation of this critique is in response to the external review draft *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children* issued by the United States Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Atmospheric and Indoor Air Programs, Washington, DC 20460.

The principal focus of this critique is on Chapters 3 and 4 of the EPA document. In particular, this critique is an assessment of the epidemiologic evidence of lung cancer from environmental tobacco smoke (ETS) and the estimates of relative risk from the epidemiologic data.

The question which is raised is whether any direct evidence exists for the relationship between ETS exposure in the general population of the United States and its implications for the public health of the nation. To address this question, a review and analysis are provided of the existing epidemiologic studies in which individuals, both cases and controls (noncases), who have higher

ETS exposures are compared to those with lower exposures, both cases and controls. Typically, the study subjects are married women who presumably never smoked but are married either to a smoker (higher exposure) or a nonsmoker (lower exposure).

The methodology in the document is a meta analysis of 21 case-control studies involving married women both exposed and unexposed to ETS. These studies are derived from the literature and have taken place world-wide during the last 15 years.

In an article by Fleiss and Gross (1991), the authors indicate that meta analysis, a set of statistical tools for combining and integrating the results of independent studies of a given scientific issue (ETS exposure in this case), can be useful when stringent conditions under which such integration is valid are met. The conditions that need to be addressed include: The appropriate adjustment or control for the biases that frequently occur in epidemiologic studies such as sociodemographic or clinical differences among study populations, misclassification of subjects with regard to case-control status and levels of exposure, factors other than the level of exposure that may affect whether a subject is a case or a control, i.e., confounding variables and the publication bias/file drawer phenomenon wherein studies that fail to show a positive association are not published and thus are not candidates for inclusion in the meta-analysis.

It is the contention of this critique that the document in question, *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children* (referred to as the Document in the remainder of this report) fails to meet most, if not all, these requirements for the appropriate meta analysis of the epidemiologic studies in question. Furthermore, it will be demonstrated that, depending on how one proceeds with the meta analysis, the results are inconclusive at best and may lead to unwarranted and potentially frightening conclusions to the lay public without having reached these conclusions in a scientifically objective manner. For example, in Table 3-5 of the Document, a meta analysis of the 19 raw studies shows a combined relative risk (RR) for lung cancer among nonsmoking females exposed to ETS (being married to a smoking male) of 1.42 compared to nonsmoking females who are unexposed (being married to a nonsmoking male). The 95-percent confidence interval for this RR is from 1.24 to 1.63. On the other hand, the adjusted meta analysis based on Table 3-6 using the 11 studies showing 95-percent confidence intervals, i.e., omitting the studies of Lam (1985) and Shimizu et al. (1988) (as the Document does) produces an RR of 1.17 with a 95-percent confidence interval from 0.99

to 1.63. Such a conclusion is consistent with the null hypothesis that there is no association between exposure to ETS and the prevalence of lung cancer. Using the DerSimonian-Laird test for homogeneity of studies, $X^2 = 13.46$, $df = 10$, $p > 0.10$, indicating relative homogeneity, numerically*, among studies. (See DerSimonian and Laird (1986) or Fleiss and Gross (1991) for details.) Thus, the two major tables for meta analysis purposes report somewhat conflicting results with regard to the purported association between nonsmokers' exposure to ETS and the prevalence of lung cancer.

Finally, it is interesting to note that in the Document no meta analysis of the corresponding male exposure data was attempted. Perhaps it was omitted because, as the Document states on p. 3-14, "Data on males is sparse by comparison ..." However, there are six studies on nonsmoking males with lung cancer who were exposed or unexposed to ETS as in the female studies; i.e, the exposed group consists of nonsmoking men married to smoking women and the unexposed group consists of nonsmoking men married to nonsmoking women. Using the notation of the Document, these studies are AKIB, BROW, BUFF, CORR, KABA, and LEE. A meta analysis of these six studies provides an RR for males of 1.14 with a 95 percent confidence interval from 0.61 to 2.16. The DerSimonian-Laird test for numerical homogeneity of studies shows $X^2 = 3.136$, $df = 5$, $p > 0.10$, indicating that the male studies are relatively homogeneous. One sees that there is no evidence whatsoever of an association between ETS exposure and the prevalence of lung cancer in males.

II. Study Biases

As pointed out in the introduction, appropriate adjustment or control for the biases that frequently occur in epidemiologic studies is necessary before analyses of these studies can proceed and the results of these analyses be interpreted properly. As Fleiss and Gross (1991) (referred to as F-G) indicate, the major potential biases in epidemiologic studies include: (i) sociodemographic or clinical differences among study populations; (ii) misclassification of subjects with regard to case-control status and levels of exposure; (iii) other confounding factors such as the age and sex of the study subjects; and (iv) the publication bias in which studies that

* This does not imply necessarily homogeneity of study methods, only their numerical homogeneity of study results.

show no association or a negative association are not published in the available literature and hence never have the opportunity of being included in an analysis of the epidemiologic studies readily accessible.

It is important to comment on how these biases are addressed in the Document. In the first place, due to the inclusion of worldwide epidemiologic studies on the relationship of ETS exposure and the prevalence of lung cancer, one would assume that the Document would have included a detailed description of the existing cultural as well as socioeconomic differences among the populations studied. No such description was found in the Document. It is well-known, for example, that living conditions differ in different part of the world. Living space is more limited in Europe and Asia that it is in North America. Moreover, Asian women tend to prepare more fried food than do their European and American counterparts. Thus, fumes from cooking oils as well as coal stoves (which are still fairly common in both Europe and Asia) contribute to environmental smoke in these non-North American settings. Another major difference among the three cultures is in the brands of cigarettes smoked. These, of course, differ from culture to culture. Also, with regard to living quarters in the three separate cultures, it is very common in Asia for elderly parents or in-laws (or both) to dwell in the same residence as the wife who may not only be exposed to her spouse's ETS but, also, to ETS from a smoking father or father-in-law. An attempt is made on p. 3-13 of the Document to quantify the percentage of controls exposed to ETS by study which, by the way, shows a threefold increase from minimum to maximum exposure. However, cultural exposure differences are not discussed. Finally, there are clear genetic differences among the three populations. It is quite possible that particular ethnic groups are more susceptible to lung cancer, independent of environmental factors, than other ethnic groups. This issue also is not addressed in any detail. What one does read on p. 3-12 is the rather remarkable statement, however, "Study differences do not invalidate statistically testing the hypothesis that exposure to ETS is unrelated to lung cancer occurrence."

Considerably more attention is paid to the issue of misclassification of smoking status. In particular, the status of the female subjects, both controls and cases, is discussed. A formula is developed in Appendix B to correct for misreporting current smokers (CS) and former smokers (FM) as never smokers (NS). The appendix itself contains much detail and does not, at this time, permit an extensive review. However, the results of this so-called "reduction formula" do not seem to have been applied in the analyses of the epidemiologic studies. Instead, a sensitivity

analysis is performed to demonstrate, under a "worst-case" scenario, that the observed RR from epidemiologic data still indicates a statistically significant association between ETS exposure and the prevalence of lung cancer in nonsmoking females. The fact remains, however, that a misclassification bias in smoking status exists in all studies, and the fact also remains that it is more likely that a current smoker or a former smoker is misclassified as a never-smoker than for the never-smoker to be misclassified as a former smoker or current smoker. It should be noted that the Document acknowledges this fact on p. 3-12 as it states: "A few studies include former smokers as nonsmokers if they have abstained from tobacco usage for some minimum period while others do not. Classification of a subject as ETS-exposed depends on the questions asked which differ across studies." Such an admission of study-to study heterogeneity is rather interesting in view of the fact that meta analysis is subsequently used to combine results of studies.

Another issue concerning misclassification is the definition of "exposed" versus "unexposed" individuals. On p. 3-12 one reads: "The relative risk comparison of exposed to unexposed individuals, however, is implicitly a comparison of 'exposed to both background and spousal smoke' to 'exposed to background only'." Although this issue is dealt with in the Document and has been dealt with in the NRC (1986) report, the way in which this is treated, i.e., assuming that an individual with both background and spousal exposure to ETS has three times the amount of ETS exposure as only background exposure, (NRC (1986) report, p. 291) in no way pertains to the individual studies. It is merely a macro-adjustment applied to all studies simultaneously, not a fine tuning of individual studies. One can easily envision situations in which an "exposed" individual is much less "exposed" than the so-called "unexposed" individual. For example, an "exposed" female may be a housewife whose smoking husband travels a great deal and hence her primary exposure may be only on weekends when they are together. On the other hand, a "nonexposed" female may work in an area where there is some moderate exposure to ETS and on weekends her primary nonexposure may take place when she is not at work and with her nonsmoking spouse.

As F-G point out, other confounding variables should be accounted for and adjusted in preparation for performing a meta analysis on epidemiologic studies. As one scans Table 3-1 in the Document (pp. 3-2 - 3-4, inclusive) it becomes clear that variables on which the final sample is matched differ considerably over the different studies. Primarily, however, age and sex are matched. However, some important potentially confounding variables such as ethnicity, place

of residence, socioeconomic status, and type of control subject are not matched in the individual studies. Moreover, the matching on sex is done by restricting the study to female subjects. However, if the male studies are considered by themselves, it was shown in the introduction that no statistically significant association exists between exposure to ETS and lung cancer prevalence.

III. Comparison of Meta-Analyses

Although not all biases can be accounted for or eliminated, F-G nevertheless believe that it is important to restrict a meta analysis of ETS exposure and risk of lung cancer in nonsmoking subjects to the studies done in the USA. As they state: "There are many reasons for restricting attention to American studies of whether there is an elevated risk to nonsmokers exposed to ETS relative to nonsmokers not so exposed. One is that this is the population on whom policy decisions will be based, and to whom those decisions will apply. Another is that the summary odds ratios in
the individual studies are derived from distributions of smoking amounts and durations, and of brands of cigarettes and other tobacco products, that pertain to populations within the United States, and may thus be expected to be relatively homogeneous. Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S. and thus odds ratios may not be relevant to the American experience. Genetic and lifestyle differences between the U. S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U. S. studies."

The nine U. S. studies in the F-G meta analysis are eight case-control studies identified in Tables 3-5 and 3-6 of the Document, which are BROW, BUFF, CORR, GARF, HUMB, KABA, VARE, and WU. The ninth study is the cohort study of Garfinkel (1981). As these studies are all well described in both the Document and F-G, only the results of their meta analyses are presented here. Using the method of analysis in F-G (which is also used in the other meta analyses in this report), the overall RR for the nine American studies is 1.12 with a 95 percent confidence interval from 0.95 to 1.30. The DerSimonian-Laird test for homogeneity yields $X^2 = 5.46$ with $df = 8$, $p > 0.10$, indicating relative numerical homogeneity from study to study within the U.S. epidemiologic studies. Thus, based on all the available American epidemiologic evidence, there is no scientific basis for concluding, as was done in the Document, that (i) there is

an association between exposure to ETS and the risk of lung cancer in the nonsmoking population in the Untied States, and, hence, that (ii) ETS is responsible for 3,800 lung cancer deaths among nonsmokers in the United States annually.

IV. Other Issues

In this section of the critique, specific points made in the Document, or specific statistical procedures that are open to question, are discussed. Unfortunately, time does not permit a complete review of all of the methodology presented in the Document.

First of all, on p. 1-4 it is stated: "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." If the dose-response issue is to be addressed, then why wasn't the other major cohort study by Garfinkel (1981) also referred to at this point? Perhaps the reason is that no clear dose-response relationship was shown in the Garfinkel study and, in fact, the RR is 1.27 for women whose husbands smoked between one and 19 cigarettes a day and 1.10 for women whose husbands smoked a pack a day or more. Neither RR is statistically significant. Furthermore, the Hirayama study has been widely criticized in the literature for its many design flaws. For example, see Kilpatrick (1989).

Next, on p. 3-21 one reads: "Table 3-1 identifies the studies with results adjusted for other variables. Some authors have not included complete details, so the choice of studies for inclusion in this section may be subjective." Many of the so-called "statistically significant" studies that are included, such as AKIB, BUFF, CHAN, CORR, GENG, KABA, KOO, LAMT, AND TRIC, did not adjust for many of the possibly confounding covariables. As was earlier discussed, combining unadjusted studies or studies in which confounding variables are not or cannot be controlled cannot be justified scientifically.

On p. 3-22 the following passage appears: "The values of S are displayed in Table 3-6 and plotted in Figure 3-3. Five of the studies had significant values of S ($p < 0.05$). The probability of observing five or more Type I errors in 11 independent studies is less than 0.001. Thus, it is highly unlikely so many significant test results would be observed if there were, in fact, no association between ETS exposure and lung cancer incidence." The 95-percent confidence

intervals indicate an entirely different situation. Only one study, that of Inoue and Hirayama (1988), demonstrates a 95-percent confidence interval that excludes unity. This event can happen by chance alone, assuming the null hypothesis of no association between ETS exposure and lung cancer incidence in nonsmokers, about 43 percent of the time, i.e., $p = 0.43$, hardly a finding inconsistent with the hypothesis of no association between ETS exposure and the incidence of lung cancer in nonsmokers. Also, with regard to the application of the S statistics, one reads on p. 3-22: "The Wilcoxon signed-rank test was also applied to the S statistics of Table 3-6 as conducted previously with the raw data, to provide another statistical test of the null hypothesis. The outcome is significant ($p = 0.014$)." The combining of the S statistics to obtain a composite statistic is done incorrectly because all S statistics are given the same weight regardless of sample size. Thus, the S statistic in a small study receives the same weight as the S statistic in a large study. For example, the largest study (Varela, 1987) receives the same weight as the study by Inoue and Hirayama (1988) which is a small study. The only correct method of combining study results (if they are combinable) is to weight them properly by their size. The next comment of interest appears on p. 3-22 as well: "No multiple comparison adjustment is necessary because the choice of a single exposure level is made without regard to statistical significance. Test results reported at exposure levels other than the one used are not relevant and no adjustment for multiple comparison is needed." This statement requires considerable clarification. To this point, not much is written concerning exposure levels. At the very least, Layard (1989) points out that in the Garfinkel (1981) study: "Women whose husbands smoked 20 or more cigarettes per day had a lower relative risk (1.10) than those whose husbands smoked 1-19 cigarettes per day (1.27)." Concerning levels of exposure and the attempt in the Document to show an increasing relative risk with an increasing level of ETS, one reads on p. 3-25: "For example, the estimated RRs increase in seven studies: AKIB, CORR, GAO, GENG, PERS, AND TRIC; decrease slightly in one case, LEE; and are variable in the remaining five plots, GARF, HUMB, KOO, LAMT, and VARE." Further on, it states: "The observed RR at the highest exposure level is less than one in only two of the 13 studies above. The probability of two or fewer such occurrences by chance alone is approximately 0.012." It should be noted, rather strongly, that the lower confidence limit at the highest level of ETS exposure is less than unity in the following studies: AKIB, HUMB, KOO, LEE, and VARE. No mention is made of those studies showing a reversal of trend, or how large the sample size is in those studies where the RR exceeds one in the groups with the highest ETS exposure.

The next issue that is of concern is the accurate diagnosis of disease. For example, if lung cancer is the disease of study (as it is here), then misclassification due to diagnosis is an important issue. To this end one reads on p. 3-33: "Some studies addressed this issue by including only pathologically confirmed lung cancers or by considering histological cell type in their analyses (e.g., CORR, GARF, PERS and others)." The statement is imprecise. We are given a few studies where one or the other of these important issues is discussed. Cell type is of critical importance because lung cancer occurring in nonsmoking individuals is usually adenocarcinoma, which is not the primary cell type for smoking individuals. It is clear that the case-control studies set out for analysis in the Document have not all been looked at from the standpoint of including only pathologically confirmed lung cancers and giving a breakdown of the lung cancer types.

Another potential source of bias that the Document attempts to address is that of surrogate responders.* One reads on p. 3-33: "The recent study by Cummings et al. (1989a) of the passive smoking histories of 380 NS further supports that conclusion. They report substantial agreement between subjects and surrogates on most exposure measures." In the first place, this study took place at Rosewell Park, which has been a major cancer treatment center for many years. Can its findings be generalized to all the epidemiologic studies presented in the Document? Even in this report, differences between subjects and surrogates exist. For example, the childhood exposure index showed a relative difference of 21 percent between subjects and surrogates. The adult index shows similar problems. Finally, in their conclusion Cummings et al. (1989a) state: "However, it should be kept in mind that while our findings suggest self-reports of exposure to passive smoke can be reproduced by surrogates, we cannot claim that our exposure measures accurately reflect 'true' exposure to tobacco smoke."

Finally, with regard to publication bias, the Document states on p. 3-33: "Wells (1989a) reviewed the subject and found it unlikely that publication bias has any substantial effect on the RRs that have been calculated from published reports for passive smoking for either men or women." Wells' review of the issue of publication bias is hardly definitive and certainly is not the "last word" on the subject. Wells agrees with Vandenbroucke (1988) that data on males are sparse and that there is danger in attempting to extrapolate a relative risk for males based on few data.

* No breakdown of surrogates is given. That is, we are not informed as to the relationship of the surrogate to the patient.

Data for males, as is shown in this critique, are no longer that sparse and some inference can be and is drawn from them. Although Wells attempts to refute Vandenbroucke's arguments in favor of a publication bias, it is somewhat curious when Wells writes: "If any investigators have data on passive smoking, however, particularly for men, that have not been published or that they have not been able to get published, I would be interested in receiving them for a possible subsequent report."

V. Conclusions

The Document appears to be an attempt by the EPA to justify and extend the findings in the NRC (1986) report in which a purported association exists between the exposure to ETS and the risk of lung cancer in nonsmoking females. Assuming this to be one of the major goals of the Document, it again fails to demonstrate any such association, as does the NRC report. Similar criticisms still exist concerning the findings with respect to this so-called "association." The principal tool that is used to attempt to justify this "association" is meta analysis. To reiterate Fleiss and Gross (1990): "Meta analysis, a set of statistical tools for combining and integrating the results of independent studies of a given scientific issue can be useful when the stringent conditions under which such integration is valid are met." The Document failed to meet these stringent conditions.

References

Akiba, S.; Kato, H.; Blot, W. J. (1986) Passive smoking and lung cancer among Japanese women. Cancer Research, 46:4804-4807.

Brownson, R. C., J. S.; Keefe, T. J.; Ferguson, S. W.; Pritzl, J. A. (1987) Risk factors for adenocarcinoma of the lung. Am. J. Epidemiol. 125:25-34.

Buffler, P. A.; Pickle, L. W.; Mason, T. J.; and Contant, C. (1984) The causes of lung cancer in Texas. Mizell, M. and Correa, P., eds. Lung Cancer: Causes and Prevention. New York: Verlag Chemie International, pp. 83-99.

Chan, W. C.; Fung, S. C. (1982) Lung cancer in non-smokers in Hong Kong. Cancer Campaign, Vol. 6, Cancer Epidemiology, (Grundmann, E., ed.) Gustav Fischer Verlag, Stuttgart pp. 199-202.

Correa, P.; Fontham, E.; Pickle, L.; Lin, Y.; Haenszel, W. (1983) Passive smoking and lung cancer. Lancet 2:595-597.

Cummings, K. M.; Markello, S. J.; Mahoney, M. C.; Marshall, J. R. (1989a) Measurement of lifetime exposure to passive smoke. Am. J. Epidemiol. 30:122.

DerSimonian, R.; Larid, N. (1986) Meta-analysis in clinical trials. Controlled Clin. Trials 7:177-188.

Environmental Protection Agency (1990) Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children. EPA External Review Draft 600/6-90/006 A.

Fleiss, J. L.; Gross, A. J. (1991) Meta analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer. A critique. Journal of Clinical Epidemiology, 44:127-139.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J. Nat'l. Cancer Inst. 6:1061-1066.

Garfinkel, L.; Auerbach, O.; Joubert, L. (1985) Involuntary smoking and lung cancer: a case-control study. J. Nat'l. Cancer Inst.75:463-469.

Geng, G.; Liang, Z. H.; Zhang, G. L. (1988) On the relationship between smoking and female lung cancer. In: Smoking and Health, Elsevier Science Publishers, pp. 483-86.

Hirayama, T. (1984) Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev. Med. 13:680-690.

Humble, C. G.; Samet, J. M.; Pathak, D. R. (1987) Marriage to a smoker and lung cancer risk. Am. J. Public Health 77:598-602.

Inoue, R.; Hirayama, T. (1988) Passive smoking and lung cancer in women. In: Smoking and Health. Elsevier Science Publishers, pp. 283-285.

Kabat, G. C.; Wynder, E. L. (1984) Lung cancer in nonsmokers. Cancer, 53:1214-1221.

Kilpatrick, S. J. (1989) Model Specifications in ETS/Nutritional Research. Indoor Air Quality (Proceedings of the International Conference, Tokyo) pp. 256-271. Springer-Verlag, Berlin.

Koo, L. C. ; Ho, J. H.; Saw, D.; Ho, C. Y. (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int. J. Cancer, 39:162-169.

Lam, T. H.; Kung, I. T. M.; Wong, C. M.; Lam, W., K.; Kleevens, J. W. L.; Saw, D.; Hsu, C.; Seneviratne, S.; Lam, S. Y.; Lo, K. K.; Chan, W. C. (1987) Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Br. J. Cancer, 6:673-678.

Lam, W. K. (1985) A clinical and epidemiological study of carcinoma of lung in Hong Kong. Thesis submitted to the University of Hong Kong for the degree of Doctor of Medicine.

Layard, M. (1989) Environmental tobacco smoke and cancer: The epidemiologic evidence. Chapter 6 in Environmental Tobacco Smoke. Proceedings of the International Symposium at McGill University, Montreal.

Lee, P. N.; Chamberlain, J.; Alderson, M. R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br. J. Cancer, 65:97-105.

Lee, P. N. (1988) Misclassification of smoking habits and passive smoking. Springer Verlag, Berlin.

National Research Council (NRC) (1986) Environmental tobacco smoke: Measuring exposures and assessing health effects: National Academy Press, Washington, D. C.

Pershagen, G.; Hrubec, Z.; Svensson, C. (1987) Passive smoking and lung cancer in Swedish women. Am. J. Epidemiol. 125(1):17-24.

Shimizu, H.; Morishita, M.; Mizuno, K.; et al. (1988). Case-control study of lung cancer in nonsmoking women. (1988) Toboku J. Exp. Med. 154:389-397.

Trichopoulos, D. (1988) Passive smoking and lung cancer. Scand. J. Soc. Med. 16:75-79.

Trichopoulos, D.; Kalandidi, A.; Sparros, L. (1983) Lung cancer and passive smoking: conclusion of Greek study. (Letter) Lancet, 667-668.

Vandenbroucke, J. P. (1988) Passive smoking and lung cancer: a publication bias? Br. J. Med. 296:391-392.

Varela, L. R. (1987) Assessment of the association between passive smoking and lung cancer. Dissertation to Yale University in candidacy for the degree of Doctor of Philosophy.

Wells, A. J. (1988a) Re: Passive smoking and lung cancer: a publication bias? (Letter) Br. Med. J. 296:1128.

Wu, A. H.; Henderson, B. E.; Pike, M. D.; Yu, M. C. (1985) Smoking and other risk factors for lung cancer in women. J. Nat'l. Cancer Inst. 74(4):747-751.

A Critique of
EPA External Review Draft
600/6-90/006A,
May 1990

Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

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The EPA draft focuses solely on the carcinogenic potential of environmental tobacco smoke (ETS) and its adverse effects on the respiratory system of children. Relevant epidemiologic control and cohort studies are reviewed, a meta-analytical approach is described to evaluate the studies together; applied mathematical formulas, dosimetric considerations of ETS and alternative approaches for estimation of lung cancer deaths due to ETS are appended. Two prior publications, the U.S. Surgeon General's Report on the Health Consequences of Involuntary Smoking (1986) and the NRC report on Environmental Tobacco Smoke (1986) are frequently cited and used as background material to support the major conclusions of this document. These conclusions are: 1) active smoking is causally associated with lung cancer in adults; 2) exposure of young children to ETS from parental smoking, in particular mother's smoking, is associated with a number of adverse effects in the respiratory tract of the children, including acute lower respiratory tract infections, respiratory tract irritations, and reduced lung function. In contrast to the pulmonary carcinogenic effects of ETS, a causal relationship between ETS exposure and children's adverse respiratory effects was not concluded. Based on these analyses and following U.S. EPA guidelines for carcinogenic risk assessment, EPA concludes that ETS is a Group A (known human) carcinogen.

Critical Review

Introduction: The EPA draft, hereafter referred to as the Draft, may be viewed as an update of the reports of NRC and the U.S. Surgeon General mentioned above, including new data which have appeared since 1986. While many of the relevant issues are more or less extensively addressed in this document, several other important areas are only superficially mentioned or not at all, and it would be useful to include these for a better understanding of problems related to effects of ETS on the respiratory tract of nonsmokers. Furthermore, the reader of the Draft gets the impression that its authors started out with a preconceived opinion about a positive and causative correlation between ETS exposure and lung cancer induction in persons so exposed and that consequently this biased opinion limits an objective discussion in many parts of the document. The following general and specific remarks are intended to point out the shortcomings and to suggest additions or a revised version of the Draft to improve its understanding for the uninformed reader and its acceptability for the scientific community.

General

My own expectation bias—prior to reading specific relevant studies—was that ETS should be regarded as a weak human lung carcinogen. This was not simply based on a similarity between ETS and mainstream smoke (MS). Actually, the two forms of cigarette smoke are dissimilar in many respects which should be made clear in the Draft—but more specifically on the fact that ETS contains known carcinogens—such as PAH and nitrosamines—and respiratory tract irritants—such as aldehydes—as well as particles which could act as carriers to distribute and deposit these potentially toxic and carcinogenic chemicals deep into the respiratory tract. In addition, the fact that MS smoking has clearly been linked with lung cancer in epidemiological studies and a causal relationship between active smoking and lung cancer is universally accepted in the scientific community, contributes to the plausibility of the link between ETS and human lung cancer if exposure to ETS is high enough (see, however, comments below). Because exposure to ETS is definitely much lower than to MS, and because deposition in the respiratory tract is quite different, only a weak positive correlation between ETS and lung cancer would be expected which may be hard to detect in epidemiological studies.

Indeed, the case-control studies cited in the EPA document do not uniformly show a significant correlation, and even reversed dose response correlations were found. Of the two large cohort studies, only the Hirayama study (exposed Japanese women) showed a significant correlation and dose-response relationship, whereas the Garfinkel study (American women) did not find a significantly elevated lung cancer risk and no dose-response relationship.

Such results would be expected of a weak pulmonary carcinogen, weak in the sense that exposure and the resulting doses in the respiratory tract are generally rather low. This result is reminiscent of epidemiological studies in diesel-exposed populations where results were either equivocal or did reveal only a weak positive, albeit significant, correlation. Collectively these diesel studies were reviewed by IARC (1989) as showing a positive correlation. However, there were uncertainties about the exposure assessment. Therefore, the overall evidence that diesel exhaust is a human lung carcinogen was termed limited.

With respect to ETS, EPA comes to a different conclusion, based mainly on a meta-analytical evaluation of the case-control studies described in the Draft and on the plausibility of causal

association. Perhaps not surprisingly, when these case-control studies—which individually did not uniformly show a significant correlation between lung cancer and ETS exposure to spousal smoking—were subjected in the Draft to meta analysis they showed a significant correlation with this combined approach.

Because I do not regard myself as an expert of meta-analytical methodology, I cannot comment thoroughly on the specific mathematical methodology applied by EPA to the case-control studies. It appears to be reasonable. However, because the individual epidemiological studies were not conducted using the same or at least a similar study protocol and because they differed in their quality, each being afflicted with certain limitations, I am surprised that these studies were used without setting certain criteria regarding a study's acceptance for such analyses prior to initiating it. For example, is the collection of data comparable (assessment of exposure), have the studies undergone peer review in the literature (inclusion of dissertations?), were attempts made to correct for misclassification, was the definition of lung cancer used in the same way in the different investigations (inclusion or exclusion of adenocarcinoma, adenocarcinoma only, etc.), was workplace co-exposure considered? I think, studies subjected to meta analysis should be of equal quality and should have used comparable methodologies when they are weighted equally in a combined analysis. Differences in research quality among the different studies must be considered (see: Bangert-Drowns, 1986). Should any study suffering from flaws that may obscure ETS effects be rejected? Possibly yes. "Criteria for study inclusion must be so explicitly stated that others may replicate the results or evaluate limitations of the study" and "the meta-analyst must test to determine whether differences in quality are related to differences in outcome" (Bangert-Drowns, 1986) might be some principles of meta analysis to be discussed at a workshop. Holding an expert workshop on meta analysis would be useful and should result in valuable recommendations about meta-analytical methodology of epidemiological studies dealing with ETS.

Thus, it would be extremely desirable and necessary to repeat the meta analysis of the case-control studies according to scientifically acceptable and defendable methodology. Without meta analysis, the results of the different epidemiological case-control studies used in the Draft do not provide sufficient evidence for a causal association between lung cancer and passive smoking as is required for classification of a Group A carcinogen (The Risk Assessment Guidelines of 1986, EPA/600/8 87/085, 1987). Rather, this evidence should be termed limited, with ETS being categorized as a probable human lung carcinogen (Group B-1). This assessment is based on

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In this context, the negative outcome of the Garfinkel cohort study should not be played down as is done repeatedly in the Draft. Quite the opposite, it should really be emphasized because it may indeed reflect a lower potency of ETS from exposure to spousal smoking in the US population due to US specific exposure conditions. This is in line with the negative results of the Janerich *et al.* study in most of their study cohorts except the group exposed from childhood on.

In summary, the *possibility* cannot be ruled out that ETS is a pulmonary carcinogen; however, collectively the results of the epidemiological studies do not support the conclusion of EPA's Draft of *sufficient* evidence for a carcinogenic potential. Finally, experts of the field of meta analysis should re-analyze the available studies with appropriate methodology to strengthen the basis for classification of ETS.

The plausibility of a correlation between ETS exposure and lung cancer which is based on the well-accepted data from mainstream smoke (MS) exposure (active smokers) becomes less obvious upon further analysis of several underlying issues:

1) Differences in respiratory tract dosimetry between ETS and MS exposure. On the one hand, we are dealing with high concentrations of particle clouds (MS), and on the other hand, with much lower concentrations of diluted smoke (ETS); breathing patterns during exposure to both forms of smoke are quite different; in addition, gas phase components also change (example, nicotine). As a result, bronchial and deep lung deposition of the respective particles change quite significantly which will be discussed in more detail under the heading Specific Comments. Such differences also make the cigarette equivalent approach questionable. (As part of the dosimetry issue, low-dose extrapolation also needs further discussion.)

2) Effects of freshly generated smoke (MS) vs. aged smoke (ETS). For example, do short-lived radicals play a role? Is there a phenomenon similar to polymer fume fever, where freshly generated fumes are highly toxic only during the first one or two minutes after their generation?

3) Location and histology of lung tumors: There is a prevalence of more central, bronchogenic lung tumors in MS smokers vs. more peripheral tumors (adenocarcinoma) in nonsmokers (Kuller *et al.*, 1986) and it appears that there is no consensus among the different investigators which tumor type is prevalent in ETS exposed people. Authors of the different epidemiological

studies have different opinions. Based on dosimetry (see above) and on the fact that chronic bronchitis in active smokers may be a significant pathogenetic event in MS-induced lung cancer, one would expect that the two exposure modes (MS vs. ETS) lead to different target sites of tumor induction in the respiratory tract. Such distinction would be important and would make it less obvious to use results from MS exposure to extrapolate down to ETS effects. On the other hand, there is the issue of a possible "metabolic overload", i.e., the high concentrations and doses of carcinogens in inhaled MS as opposed to much lower concentrations in inhaled ETS. It is conceivable, as shown for BaP by Wolff *et al.* (1989), that high doses of BaP arriving at a target cell over a short period of time may overwhelm the cell's ability to metabolize BaP and to form carcinogenic metabolites. Instead, much of the BaP is quickly cleared via the blood circulation (Wolff *et al.*, 1989). Apparently, the dose delivery rate of a carcinogen to the cell is an essential parameter as can be deduced from results on the formation of BaP metabolites after inhalation of the pure compound vs. inhalation of BaP plus carbon black particles (Sun *et al.*, 1984; Bond *et al.*, 1986). In the latter case, binding of BaP with macromolecules was increased 10-to 20-fold.

4) Experience and results from epidemiological and experimental studies on the carcinogenic effects of diesel exhaust may also question the plausibility of a correlation between inhaled organic carcinogens and lung tumors: the tumor-inducing potential of inhaled diesel exhaust can probably be explained by a pure particle effect (see attached manuscript by Oberdörster and Yu). However, further studies on the inducibilty of DNA-adducts in the lung may still reveal a possible contributory effect of organic components.

It would be useful to include a discussion of the issues addressed in the previous paragraph in a revised version of the EPA document. This would show that difficult issues related to the possible carcinogenic effects of ETS have been addressed objectively from different viewpoints. The present Draft is obviously a first attempt to deal with the difficult questions related to the carcinogenic potential of ETS exposure. An inclusion of the recommended changes and topics outlined in these comments would strengthen the document.

Attention should also be drawn to the afore mentioned recent paper by Janerich *et al.* mentioned before (N. Engl. J. Med. 323:632-636, 1990: Lung cancer and exposure to tobacco smoke in the household. Published based on dissertation by Varela, 1987). The authors of this study report that only exposure during early life (childhood and adolescence, less than 21 years of age)

smoker years significantly increased the risk of lung cancer (doubled it to 2.07), but exposure during adulthood (more than 21 years of age) had no significant effect on lung cancer. While recall bias may have influenced the result, as discussed by the authors, the study seemed otherwise well conducted and should be included in a meta-analysis approach. Finally, it would be useful to include a table at the end of Section 4 which shows the possible carcinogenic potency of ETS in relation to other carcinogenic compounds, as is done in other Health Criteria Documents (unit risk estimate). The derivation of such unit risk for ETS may be difficult due to the limited data base. However, this would give the reader a perspective about the ranking of ETS among other inhaled carcinogens.

The section on respiratory illness in children (respiratory symptoms; acute respiratory illness; impaired pulmonary function) addresses adequately possible confounding variables and biases of the different epidemiological studies. It would be useful and strengthen the document, however, to include (perhaps as an Appendix) a more detailed description of the individual studies referenced in this section. The conclusions in the document about a correlation between measured effects and parental, especially maternal, smoking appears to be justified. Obviously, all of the epidemiological studies have some shortcomings and one can think of several possible confounding variables which need to be investigated, such as ventilation in homes (sick-building syndrome), pets in household, crowdedness, activity of child, etc. However, the document stops short of suggesting a causal relationship between children's respiratory illness and parental smoking although in some studies family history of coughing or respiratory illness was found to have a large influence, yet could not explain all of the observed effects. Overall, this section is reasonably well written although several methodological questions still need to be discussed. Such discussion would be facilitated by the inclusion of a brief description of the studies as mentioned above. I believe the overall evidence from the different studies supports the conclusion of a correlation between ETS exposure and respiratory tract illness in children, which has important implications from a medical preventive point of view.

Specific Comments

Page 2-1, first para: ETS consists of side stream smoke (SS) and exhaled mainstream smoke (MS) which should be kept in mind throughout the document. Most of the discussion treats SS as the sole component of ETS which is not correct.

Second para: The plausibility of a carcinogenic effect of ETS, based on the known carcinogenic effect of MS exposure, is attractive and may be justifiable. However, there is also evidence that low concentrations of known organic carcinogens inhaled together with high concentrations of particles may not contribute to a tumorigenic effect and one has to be cautious not to be biased by a preconceived view when conducting or reviewing a study on the effects of ETS. For example, diesel exhaust has many known carcinogens, yet the positive (in terms of tumor induction) results in long-term rat inhalation studies with diesel exhaust very likely are not caused by the carcinogens but by the particulate phase, even without the organics. Inhalation and intratracheal instillation studies with carbon black alone without carcinogens gave similar tumor responses in rat studies. In addition, the well-known inflammatory effects in the conducting airways caused by MS may be highly contributory to tumors induced by this mode of exposure, whereas this inflammatory response is in all likelihood absent, or only present to a much lower degree, in ETS-exposed people .

Page 2-3, first para, line 3: The plausible assumptions for misreported smoking habit used in the NRC report should be described here briefly.

Page 2-4, last para: Limitations of the cigarette-equivalent approach due to incomplete knowledge of the biological basis of ETS- and MS-induced lung cancer are pointed out. This is correct, but the same cautionary note should also be applied when the plausibility of a carcinogenic potential of ETS exposure based on the MS effect is inferred, as mentioned above.

Page 3-12, first para: The last two sentences refer to background exposure with regard to the relative risk comparison of exposed to unexposed individuals. It may be conceivable, however, that background exposure may be quite different between ETS-exposed people (spouses of smokers) and unexposed. The former are more used to being exposed to an air pollutant, but the latter may be more conscious to avoid also exposures at workplace and other places. Thus, the question arises as to whether background exposure can be assumed to be the same between the two groups.

Second para: Large differences in controls classified as exposed between the different case-control studies are noted ranging from 15 to 84%. Although it is stated that such study differences do not invalidate statistically testing the correlation between ETS exposure and lung cancer, the

not invalidate statistically testing the correlation between ETS exposure and lung cancer, the question arises whether such differences may prohibit using these different studies in a meta-analytical approach. Thus, before a meta analysis (page 3-14) is performed criteria should be formulated to decide which studies fulfill these criteria and should be used in such an approach (see general comments). Letzel and Uberla (1990, see below) recently reported on their meta analysis on passive smoking and lung cancer. They insist that every meta analysis has to state its goals, criteria, and methods before it starts. Consequently, they included five criteria to conduct meta analysis of the available case-control studies under different aspects (Letzel and Uberla, 1990.) The result of their meta analysis, when using different case-control studies and when applying different criteria, is summarized as follows:

Overall risk of dying of lung cancer from nonsmoking women married to smoking men is:

1.074, based on 6 case-control studies of reasonable quality

1.013, based on 2 prospective studies, using the Hirayama study with the age selection bias removed, as shown by the authors

1.035, based on 2 prospect studies and 6 case-control studies of reasonable quality

1.076, based on 11 studies with the Trichopoulos study excluded

1.118, based on all 12 studies including the Trichopoulos study.

They found that these risk estimates are not statistically different from unity. Their results differ from that of Wald *et al.* (1986) who did not take into account the quality of the individual studies and did not perform an analysis of sensitivity. Certainly, more discussions on the use and performance of meta analysis in EPA's Draft is needed. As stated by Letzel and Uberla, "the whole question of meta analysis comes down to the question of the quality of the individual study."

Page 3-34, last para: Reference is made here to P.N. Lee's statement that there is a statistically significant association in lung cancer risk in the study of Hirayama. However, other criticisms, in particular that calling for independent public examination of Hirayama's raw data, have not been answered (Kilpatrick, 1990.)

Page 3-39, first para: Defining direct and indirect passive smoking by a given distance from the source does not necessarily give an accurate picture. Certainly the size of the room and also the ventilation rate are of great importance for exposure to passive smoke .

Page 3-43, first para: The statement that the statistical results "solidly" support the conclusion of the association between lung cancer and ETS exposure is not justified based on the individual case-control studies alone.

Second para: As mentioned before, Hirayama still needs to answer criticisms made about his study. The statement that "results of the American cohort study are *less* conclusive" is a bit misleading, it should rather read that they are *not* conclusive and do not show a correlation.

Third para: Likewise, the statement that the American cohort study "weakly" indicates an increased lung cancer risk is not supported by the results and should be changed. Such statements give the appearance of a document written with a rather biased opinion.

Page 4-13, last para: Comparing SDA cohorts to nonsmoking non-SDA cohorts with respect to lung cancer incidences implies that a possible difference is solely due to differences in ETS exposure. However, it is as likely that other differences in the lifestyles, other workplace exposures, etc., may contribute or even fully explain such possible differences.

Page 4-15, second para: The assumption of the cigarette-equivalent approach is that the lung cancer risks in passive and active smokers are equivalently indexed by a common measure of exposure to tobacco smoke, for example, use of nicotine or its metabolite cotinine. This implies: 1) lung tumors should be the same in MS smokers and ETS smokers; 2) nicotine metabolism and dosimetry should be the same in both exposure modes; 3) additional effects of MS smoke (e.g., bronchitis) do not contribute to lung cancer incidences. Probably, none of these implications is correct as discussed already before. More on respiratory tract dosimetry will be discussed later (see comments on Appendix C).

A more thorough discussion of the differences between MS and ETS dosimetry would be useful and it would be worthwhile, as stated on page 4-16, last paragraph, to further develop the knowledge base surrounding this issue. A further development of the cigarette-equivalent approach would be worthwhile only if it takes into account compound-specific dosimetry and metabolism in lungs of MS and ETS smokers. Simply taking the particulate concentration or the inhaled particulate mass or cotinine levels as measures of equivalent exposure is probably not indicated. A better justified approach has to be used.

Page 4-22, second para: When recommending to use average cotinine concentration in smokers and nonsmokers to extrapolate risk from active smoking to passive smoking, a statement or reference to another section of the document (4-15) should be included which discusses differences in dosimetry and metabolism of nicotine between MS- and ETS-exposed persons. The two final sentences of this paragraph on the non-negligibility of a positive excess risk of 1.02 and 1.07 are not understandable and need to be explained better.

Page 4-34, first para: The aforementioned different opinions regarding lung cancer types that correlated with ETS exposure become obvious here again. This topic definitely needs some more discussion in the Draft (see Kuller, 1986).

Second para: The dissertation by Varela (1987) has now been published, as mentioned before (Janerich *et al.*, 1990).

Page 4-39, last para: Consistency of response. The simple statement that the two completed cohort studies observed a higher risk of lung cancer among female never-smokers, classified as exposed to ETS, is misleading because it fails to mention in this summarizing statement that this higher risk was not significant in the Garfinkel study and, moreover, there was no increase in response with increasing exposure in that study.

Page 5-18, end of second para: Citing the increased incidence of respiratory symptoms in adult smokers as a plausible reason for such symptoms to occur in ETS-exposed children raises again the question of comparative dosimetry. Such symptoms relate to the doses to target sites which, as pointed out before, conceivably are quite different between MS and ETS exposure. However, I agree with the conclusion of the Draft, that passive smoking in early childhood is associated with respiratory illness in children so exposed. If persistent over a longer period of time, ETS exposure may indeed reduce their rate of pulmonary growth and development, although no causative association between ETS and these effects is assumed in the Draft.

Appendices

Page A-1: The question comes up here again about the histological type of lung tumors associated with ETS vs MS exposure. As indicated before, a discussion of this topic should be included

in the main text of the document. For example, is the higher relative risk found in the study by Gao *et al.* (1987) for squamous and oat-cell carcinoma indicative of active smoking, i.e., misclassification? (page A-3, first para). Quite obviously, when evaluating the individual case-control studies described here and on the following pages, there is no uniformity with regard to tumor classification by histology.

Page A-6, first para: Is "marginal significance" equivalent to being not significant? This question of tumor type associated with ETS exposure is an important one because there is great confusion, as can be seen on these pages A-2 through A-14. Differences exist among the authors of the different studies in what is regarded as typical lung cancer for ETS-exposed people. It appears that peripherally located tumors (adenocarcinoma) are more likely to occur in nonsmokers as opposed to centrally-located tumors which are typical for MS smokers. Because an active smoker is definitely also a passive smoker, one would expect to see peripheral tumors in active smokers, as indeed is the case. If peripheral tumors are most likely to occur in passive smokers, is the occurrence of centrally-located tumors in this group an indication of previous active smoking? The existing confusion on this issue becomes apparent in Appendix A which describes some of the individual case-control studies. As stated before, a discussion of the biology of lung cancer would be useful before going into the details of the epidemiological studies.

Page C-1: The reasons for inclusion of Appendix C are not obvious. In my view, they are two-fold: 1) to calculate equivalent doses for ETS and MS; 2) to point out differences in dosimetry between ETS and MS.

Page C-4, second para: The example given here is for nicotine attached to particles, as is also the case in an example given toward the end of this Appendix C. However, because nicotine in ETS is to more than 95% in the gas phase and in MS to more than 95% in the particulate phase, the dosimetries of deposited and absorbed nicotine are likely to be quite different between the two forms of smoke. Depending on water solubility and reactivity of nicotine in the gas phase, ETS nicotine may be absorbed quite efficiently in the upper respiratory tract, including the nasal-pharyngeal passages, while this is quite different for MS nicotine which may more easily travel down into the deep lung, attached to particles.

Page C-5, last para, first sentence: The meaning of this sentence is unclear. Any inhaled material will deposit onto the walls of the airways (not lungs).

Page C-6, first para: It should be considered also to express the uptake U per unit surface area of the airways which would allow a better comparison between MS and ETS, as will be shown below.

Second para: It should also be mentioned in this paragraph that newer models predicting particle deposition in the lungs, including a generation-by-generation deposition, are available. For example, models by Yeh and Schum (1980) and Schum and Yeh (1980) allow to model deposition of different particle sizes subjected to different breathing patterns in the human lung. In general, it would be useful to point out the different doses involved in a dose-response relationship in the respiratory tract, i.e., inhaled, deposited, retained doses. The deposited dose is not yet equivalent to an uptake, because many of the particles deposited will actually be eliminated from the lungs again. Uptake into lung cells involves a separate step.

Page C-8, third para: More defined models of tracheal bronchial clearance are available, for example, Yu *et al.* (1986) and Lee *et al.*, (1989).

Page C-12: This page, dealing with translocation of inhaled material to systemic organs, needs some rewriting. For example, the statement in paragraph 1 that material deposited in the pulmonary region of the lung tends to be translocated into the blood stream is only true for dissolved material and not for particles. In the second paragraph, it is suggested that material deposited in the nasal-pharyngeal region is removed primarily to the GI tract with little absorption of ETS chemicals directly into the blood stream. However, that depends on whether a chemical is in the gas or particle phase and how well it is adsorbed as a gas onto the walls of the airways. Absorption from the GI tract is different in that absorbed materials pass first through the liver. The statement that this is due to the "proximity" of the liver should be changed.

Page C-13: All arrows connecting compartments should be labeled. The arrow going from lymph nodes to excreta should be changed to going from lymph nodes to blood.

Page C-14, last para: The assumption that deposition in the NP region contributes only insignificantly to a systemic dose should not be made summarily. Gases like nicotine in ETS could very well be absorbed in this region and contribute to a systemic dose.

Pages C-18 and C-19: It appears that SS is used as a surrogate for ETS which, as mentioned before, is not correct. It should be pointed out that ETS consists of diluted SS and exhaled MS. This is an important distinction in particular with regard to an aging effect of smoke characteristics.

Page C-20, last para: References are made to values of intakes for passive and active smokers, computed and shown in Tables C-3 on page C-22. It is, however, unclear which deposition fractions for particles and gases have been used for constructing Table C-3. For example, nicotine in ETS in the vapor phase is probably readily absorbed in the nasal-pharyngeal region while, according to page C-12, there is little absorption in this region. Which respiration volume, rates, respiratory pauses, etc., were used for computing the data in Table 3 for active and passive smoking? Mouth and/or nose breathing? Although data for those parameters are given in the Appendix, it is not clear whether this table has been constructed using those data.

Page C-21, second para: This paragraph compares the relative concentrations of four chemicals in SS and ETS and concludes that these are rather similar for three of the chemicals between the two different forms of smoke. However, the question also is whether these chemicals are in the same phase of smoke, i.e., vapor or particle phase. This would be important for dosimetric calculations. However, lacking such data, it may be appropriate to use as a first approach data of SS as the surrogate for ETS after it has been made clear that there is a distinction between the two.

Page C-28, first para: The percentage of inhaled MS particles deposited in the lungs (80%) sounds rather high. It has been found to be on the average 47% by Hinds *et al.* (1983) which would also be more in line with model predictions on particle deposition. In addition, it is not quite clear what f NP implies for active smokers, there is no nasal component during active smoking except possibly for exhaled MS smoke.

Second para: The assumption that there is no hygroscopic growth of ETS particles, based on the study by Hiller *et al.* (1982), is questionable because Hiller *et al.* were working with SS, not ETS. In addition, they did not ensure that the humidity conditions in their sampling bag of exhaled air was the same as that in the respiratory tract.

Third para: I performed some model calculations on deposition of ETS and MS particles, using the EPA data set as well as slightly changed parameters, based on a modified deposition model

of Yeh and Schum. The data are shown in Tables 1-4. The predicted daily deposition is different from what is given in the EPA document, in particular for the pulmonary regions of the active and passive smoker, i.e., about half of the EPA-value for the active smoker and about twice for the passive smoker. Again, it is not clear which parameters EPA used in their model, mouth breathing vs. nose breathing, breath holding included, etc.

A comparison of attached Tables 1 and 2 shows that relative depositions throughout the respiratory tract are quite different for ETS and MS particles. For the ETS exposure, nose breathing is assumed and for MS exposure mouth breathing is assumed with a 3-second respiratory pause. Higher surface area concentrations after inhalation of MS occur in generations 3 and 4 of the conducting airways. This is consistent with prevalent sites for lung tumors (Schlesinger and Lippmann, 1979), i.e., more centrally located tumors. For ETS exposure, relative highest surface area concentrations are achieved in generations 15-18, i.e., the transitional zone of the lung where one would expect to see peripheral lung tumors to occur (bronchiolo-alveolar tumors). However, as pointed out previously, additional effects of MS exposure on the conducting airways have to be considered, i.e., bronchitis and impaired mucociliary clearance (see, for example, Vastag *et al.*, 1986). Whereas Tables 1 and 2 assume respiratory values as proposed by EPA in their document, Tables 3 and 4 apply more realistic values for tidal volumes (500 cc for ETS exposure and 1,000 cc for MS exposure) and decreased respiratory frequency (12 for MS exposure). The result is essentially similar to the previous predictions in Table 1 and 2, i.e., relatively higher surface area deposition in the upper conducting airways for MS exposure and relatively higher deposition in the transitional region (deeper lung) for ETS exposure.

One important question for such dosimetric calculations is whether the active smoker actually inhales the MS in a bolus with a volume of 35-50 cc, which is superimposed on the larger tidal volume, or whether the MS is inhaled over the total tidal volume. The former case would need some additional modeling which is presently not available in the model of Yeh and Schum, which was the basis for Tables 1-4. The paper by Muller *et al.* (1990) compares deposition predictions of different breathing rates and smoke particle sizes based on a Weibel lung model. However, their hygroscopic growth, assuming that of NaCl particles, may be too high for MS particles. Additional influences of a "cloud" effect may have to be considered too (Martonen, 1989)

In any event, the results in Tables 1-4 show that the highest surface area doses are expected to be differently located between the two exposure modes for MS and ETS and that consequently one may expect to see differences in tumor induction between active and passive smokers as indeed seems to be implied by several of the authors of the epidemiological studies. Again, parameters used in the EPA Draft to model deposition need to be clearly stated so that the reviewer can follow the calculations performed in this exercise.

Page C-30, third para: An alveolar retention half-time of 17 hours for particles in active smokers is assumed, based on results from Black and Pritchard (1984) and the same value is also assumed for passive smokers. The study by Black and Pritchard, however, is only a preliminary conference report, no detailed data are given, in particular about the persistence of the label that was used in their study. The fast dissolution of this label in lung tissue has not been demonstrated to be equivalent to MS particle dissolution. Retention half-times for particles in the alveolar region are much longer than 17 hours which represents only the short-lived fraction of dissolved particle constituents removal from the deep lung. Normal alveolar retention half-times for particles are on the order of 300-400 days (Bailey *et al.*, 1985). In active smokers the retention half-time is increased (Bohning *et al.*, 1982; Cohen *et al.*, 1979). Therefore, the retention time in the active smoker may even be longer than 300-4000 days. At any rate, the assumed 17 hours is, at present, not acceptable as an alveolar retention half-time for deposited smoke particles in this region. Consequently, values given in Table C-5 on page C-32 on particulate-phase chemicals and daily interval organ burdens could be considerably different because they are based on the very short retention half-time of 17 hours, measured for one label only.

Page C-33, second para: A discussion of nicotine absorption for active and passive smokers is included here. If nicotine in the gas phase (passive smoker) is mostly taken up in the upper respiratory tract, then there is no need to model a time for penetrating alveolar cells in the passive smoker, as done in this paragraph. Furthermore, the calculated nicotine dose to the pulmonary region is based on the assumed retention half-time of 17 hours mentioned before. In addition, both tracheobronchial and pulmonary uptake of nicotine are based on particulate deposition and retention which, as mentioned above, does not apply to gas phase nicotine in ETS. Thus, the comparison made here is not valid. The numbers given in this paragraph need additional clarification.

Page D-4, first line: The study by Grimmer *et al.* (1988) was dealing with SS not ETS. This is rectified in the listed disadvantages of the Grimmer study on page D-8, first line, but should also be made clear here.

Page D-8: It has to be kept in mind that the relative potency approach (data shown in Table D-4) implies that ETS and MS act in the same way with regard to tumor induction, an assumption which can be challenged due to the additional effects of MS caused in the respiratory tract at sites where tumors are induced, i.e., in the upper conducting airways. Thus, the relative potency estimates have to be used with caution.

Summarizing Remarks

EPA's Risk Assessment Guidelines of 1986 state that an agent should be classified as Group A–Human Carcinogen when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agent and cancer. The Draft categorizes ETS as a Group A carcinogen based on the weight of evidence from results of the epidemiological studies which is supported by the result of the meta analysis performed by EPA. However, the meta analysis performed in the Draft does not conform to scientifically accepted standards. Because of the highly variable outcome of the different epidemiological studies they do not support a statement of sufficient evidence for a causal association between lung cancer and passive smoking as is required for classification of a Group A carcinogen. Rather, this evidence should be termed limited. This would be in line with the evaluation of IARC which stated in 1987 that the available epidemiological evidence is compatible with either the presence or absence of lung cancer risk. The strongest evidence that ETS may indeed have a carcinogenic potential is given by the large Japanese cohort study (Hirayama) and by a recently published study of Janerich *et al.* In view of the negative results of other epidemiological studies, in particular the large American cohort study (Garfinkel), it appears that a carcinogenic *potential* of ETS may only be detectable under exposure conditions resulting in a sufficiently high dose. This means, on the other hand, that the carcinogenic *potency* of ETS depends very much on specific exposure conditions, a conclusion which has to be considered for quantitative risk assessment.

Thus, although the possibility cannot be ruled out that ETS is a pulmonary carcinogen, collectively, the results of the epidemiological studies do not support the conclusion of EPA's Draft

of sufficient evidence for a carcinogenic potential. In view of the difficulties to express the dose received by a passive smoker from the smoking of one cigarette (exposure of a spouse to ETS from one cigarette in a Japanese house is not equivalent—in terms of delivered dose—to exposure of a spouse to ETS from one cigarette in an American home) it is difficult, perhaps even impossible, at present to perform a meaningful quantitative risk assessment for ETS exposure.

With respect to the biological plausibility of a carcinogenic effect of ETS, which is based on the well accepted causal relationship between active smoking and lung cancer, it needs to be emphasized that there are differences between MS and ETS, and furthermore that ETS is not equivalent to SS. Aging and different gas- and particle phase composition are only one aspect of the differences, and differences in respiratory tract dosimetry are additional ones because nasopharyngeal, bronchial and deep lung deposition of ETS and MS particles are quite different. Such differences also make the cigarette equivalent approach questionable.

Because such dosimetric differences could explain a shift in tumor location from more central (MS) to more peripheral (ETS) in the respiratory tract, additional attention needs to be given to these issues in the final EPA document. This includes also the pathogenetic importance of chronic bronchial inflammatory condition in the active smoker which is in all likelihood absent in the passive smoker and which makes an extrapolation of effects of MS exposure to those of ETS exposure questionable if this extrapolation is based on the plausibility of expected similar effects. Furthermore, there is also evidence that organic carcinogens inhaled together with high inhaled particle concentrations may contribute very little or not at all to a tumorigenic effect. Thus, while the plausibility of a carcinogenic effect of ETS based on the known carcinogenic effect of MS exposure is an attractive assumption it needs further discussion of relevant underlying principles.

*** HUMAN MODEL
*** 100 % Nasal Breathing
*** Particle size (microns) = .15
*** Sigma G = 1.5
*** Tidal Volume (cm^3) = 750
*** Respiratory Frequency = 15
*** Breath-holding pause (sec.) = 0
*** Aerosol Concentration = .2 mg/m^3
*** Date: 01-17-1991; Time: 16:58:44

Table 1
ETS (EPA data)
Nose Breathing

Generation Number	Fractional Deposition	Surface Area	Surface Area at FRC	% of inhaled Aerosol deposited per cm^2	% of inhaled Aerosol deposited per cm^2 At FRC	Micrograms Deposited in 8 hr	Micrograms of Aerosol Deposited per FRC cm^2 in 8 hr.
1	2.012E-04	53.97	50.75	3.728E-04	3.964E-04	2.173E-01	4.281E-03
2	1.950E-04	32.88	31.12	5.929E-04	6.265E-04	2.106E-01	6.766E-03
3	1.720E-04	19.51	18.46	8.816E-04	9.317E-04	1.857E-01	1.006E-02
4	1.767E-04	11.51	11.14	1.535E-03	1.587E-03	1.908E-01	1.714E-02
5	2.780E-04	19.27	18.59	1.442E-03	1.495E-03	3.002E-01	1.615E-02
6	4.331E-04	41.69	39.65	1.039E-03	1.092E-03	4.677E-01	1.180E-02
7	6.204E-04	48.41	46.52	1.281E-03	1.334E-03	6.700E-01	1.440E-02
8	1.025E-03	102.20	97.27	1.003E-03	1.054E-03	1.107E+00	1.138E-02
9	1.492E-03	176.56	166.87	8.450E-04	8.941E-04	1.611E+00	9.656E-03
10	1.942E-03	193.96	184.68	1.001E-03	1.051E-03	2.097E+00	1.135E-02
11	2.673E-03	267.10	253.12	1.001E-03	1.056E-03	2.887E+00	1.140E-02
12	3.584E-03	341.10	323.04	1.051E-03	1.109E-03	3.870E+00	1.198E-02
13	4.812E-03	414.83	392.90	1.160E-03	1.225E-03	5.197E+00	1.323E-02
14	6.272E-03	498.56	472.01	1.258E-03	1.329E-03	6.773E+00	1.435E-02
15	8.181E-03	587.99	558.02	1.391E-03	1.466E-03	8.836E+00	1.583E-02
16	1.085E-02	792.81	756.21	1.369E-03	1.435E-03	1.172E+01	1.550E-02
17	1.249E-02	819.44	665.65	1.524E-03	1.876E-03	1.349E+01	2.027E-02
18	1.778E-02	1361.01	1113.50	1.306E-03	1.596E-03	1.920E+01	1.724E-02
19	2.240E-02	1870.95	1530.70	1.198E-03	1.464E-03	2.420E+01	1.581E-02
20	2.979E-02	3020.39	2471.11	9.862E-04	1.205E-03	3.217E+01	1.302E-02
21	3.755E-02	4958.69	4056.91	7.572E-04	9.255E-04	4.055E+01	9.996E-03
22	4.261E-02	8781.65	7184.65	4.853E-04	5.931E-04	4.602E+01	6.406E-03
23	3.445E-02	14723.03	12045.55	2.340E-04	2.860E-04	3.720E+01	3.088E-03
24	6.212E-03	33498.67	27406.72	1.854E-05	2.267E-05	6.709E+00	2.448E-04
25	0.000E+00	281286.70	490541.70	0.000E+00	0.000E+00	0.000E+00	0.000E+00

Percent deposited in tracheobronchial region = 4.290802
Percent deposited in pulmonary region = 20.32789
Extrathoracic deposition (percent) = 0

Mass (micrograms) deposited in airways during 8 hr:
Extrathoracic - 0.00
Tracheobronchial - 46.34
Pulmonary - 219.54

51246 0085

*** HUMAN MODEL
*** 0 % Nasal Breathing
*** Particle size (microns) = 1.4
*** Sigma G = 1.5
*** Tidal Volume (cm^3) = 750
*** Respiratory Frequency = 15
*** Breath-holding pause (sec.) = 3
*** Aerosol Concentration = 15 mg/m^3
*** Date: 01-17-1991; Time: 17:00:41

Table 2
MS (EPA data)
Mouth Breathing

Generation Number	Fractional Deposition	Surface Area	Surface Area at FRC	% of inhaled Aerosol deposited per cm^2	% of inhaled Aerosol deposited per cm^2 At FRC	Micrograms Deposited in 8 hr	Micrograms of Aerosol Deposited per FRC cm^2 in 8 hr.
1	1.762E-04	53.97	50.75	3.265E-04	3.473E-04	1.427E+01	2.813E-01
2	2.876E-03	32.88	31.12	8.746E-03	9.241E-03	2.330E+02	7.485E+00
3	3.235E-03	19.51	18.46	1.658E-02	1.753E-02	2.620E+02	1.420E+01
4	2.741E-03	11.51	11.14	2.381E-02	2.461E-02	2.220E+02	1.994E+01
5	2.835E-03	19.27	18.59	1.471E-02	1.525E-02	2.297E+02	1.235E+01
6	2.502E-03	41.69	39.65	6.001E-03	6.309E-03	2.027E+02	5.110E+00
7	2.377E-03	48.41	46.52	4.909E-03	5.109E-03	1.925E+02	4.138E+00
8	3.007E-03	102.20	97.27	2.943E-03	3.092E-03	2.436E+02	2.504E+00
9	3.477E-03	176.56	166.87	1.969E-03	2.084E-03	2.817E+02	1.688E+00
10	3.159E-03	193.96	184.68	1.629E-03	1.711E-03	2.559E+02	1.386E+00
11	4.222E-03	267.10	253.12	1.581E-03	1.668E-03	3.419E+02	1.351E+00
12	4.951E-03	341.10	323.04	1.452E-03	1.533E-03	4.011E+02	1.242E+00
13	5.717E-03	414.83	392.90	1.378E-03	1.455E-03	4.631E+02	1.179E+00
14	7.198E-03	498.56	472.01	1.444E-03	1.525E-03	5.830E+02	1.235E+00
15	7.934E-03	587.99	558.02	1.349E-03	1.422E-03	6.427E+02	1.152E+00
16	9.785E-03	792.81	756.21	1.234E-03	1.294E-03	7.926E+02	1.048E+00
17	9.223E-03	819.44	665.65	1.126E-03	1.386E-03	7.471E+02	1.122E+00
18	1.237E-02	1361.01	1113.50	9.090E-04	1.111E-03	1.002E+03	8.999E-01
19	1.570E-02	1870.95	1530.70	8.389E-04	1.025E-03	1.271E+03	8.306E-01
20	2.390E-02	3020.39	2471.11	7.911E-04	9.670E-04	1.936E+03	7.833E-01
21	3.821E-02	4958.69	4056.91	7.705E-04	9.417E-04	3.095E+03	7.628E-01
22	6.384E-02	8781.65	7184.65	7.270E-04	8.886E-04	5.171E+03	7.198E-01
23	1.000E-01	14723.03	12045.55	6.794E-04	8.305E-04	8.103E+03	6.727E-01
24	5.148E-02	33498.67	27406.72	1.537E-04	1.879E-04	4.170E+03	1.522E-01
25	0.000E+00	281286.70	490541.70	0.000E+00	0.000E+00	0.000E+00	0.000E+00

Percent deposited in tracheobronchial region = 6.619364
Percent deposited in pulmonary region = 31.47508
Extrathoracic deposition (percent) = 8.36

Mass (micrograms) deposited in airways during 8 hr:
Extrathoracic - 6771.60
Tracheobronchial - 5361.68
Pulmonary - 25494.82

51246 0086

*** HUMAN MODEL
*** 100 % Nasal Breathing
*** Particle size (microns) = .15
*** Sigma G = 1.5
*** Tidal Volume (cm^3) = 500
*** Respiratory Frequency = 15
*** Breath-holding pause (sec.) = 0
*** Aerosol Concentration = .2 mg/m^3
*** Date: 01-17-1991; Time: 17:02:24

Table 3
ETS (EPA data, lowerTV)
Nose Breathing

Generation Number	Fractional Deposition	Surface Area	Surface Area at FRC	% of inhaled Aerosol deposited per cm^2	% of inhaled Aerosol deposited per cm^2 At FRC	Micrograms Deposited in 8 hr	Micrograms of Aerosol Deposited per FRC cm^2 in 8 hr.
1	2.604E-04	52.92	50.75	4.921E-04	5.131E-04	1.875E-01	3.694E-03
2	2.404E-04	32.31	31.12	7.441E-04	7.725E-04	1.731E-01	5.562E-03
3	2.080E-04	19.17	18.46	1.085E-03	1.127E-03	1.497E-01	8.112E-03
4	2.149E-04	11.39	11.14	1.886E-03	1.930E-03	1.547E-01	1.390E-02
5	3.413E-04	19.06	18.59	1.791E-03	1.836E-03	2.458E-01	1.322E-02
6	5.365E-04	41.03	39.65	1.307E-03	1.353E-03	3.863E-01	9.741E-03
7	7.684E-04	47.81	46.52	1.607E-03	1.652E-03	5.532E-01	1.189E-02
8	1.263E-03	100.60	97.27	1.256E-03	1.299E-03	9.096E-01	9.352E-03
9	1.822E-03	173.41	166.87	1.051E-03	1.092E-03	1.312E+00	7.863E-03
10	2.344E-03	190.96	184.68	1.228E-03	1.269E-03	1.688E+00	9.138E-03
11	3.179E-03	262.56	253.12	1.211E-03	1.256E-03	2.289E+00	9.042E-03
12	4.196E-03	335.23	323.04	1.252E-03	1.299E-03	3.021E+00	9.353E-03
13	5.544E-03	407.70	392.90	1.360E-03	1.411E-03	3.991E+00	1.016E-02
14	7.109E-03	489.93	472.01	1.451E-03	1.506E-03	5.118E+00	1.084E-02
15	9.118E-03	578.27	558.02	1.577E-03	1.634E-03	6.565E+00	1.176E-02
16	1.187E-02	780.77	756.21	1.520E-03	1.569E-03	8.545E+00	1.130E-02
17	1.315E-02	769.93	665.65	1.708E-03	1.975E-03	9.467E+00	1.422E-02
18	1.828E-02	1281.20	1113.50	1.427E-03	1.642E-03	1.316E+01	1.182E-02
19	2.227E-02	1761.23	1530.70	1.265E-03	1.455E-03	1.604E+01	1.048E-02
20	2.802E-02	2843.27	2471.11	9.856E-04	1.134E-03	2.018E+01	8.165E-03
21	3.175E-02	4667.90	4056.91	6.803E-04	7.827E-04	2.286E+01	5.635E-03
22	2.689E-02	8266.68	7184.65	3.253E-04	3.743E-04	1.936E+01	2.695E-03
23	6.056E-03	13859.65	12045.55	4.369E-05	5.027E-05	4.360E+00	3.620E-04
24	0.000E+00	31534.26	27406.72	0.000E+00	0.000E+00	0.000E+00	0.000E+00
25	0.000E+00	264791.60	490541.70	0.000E+00	0.000E+00	0.000E+00	0.000E+00

Percent deposited in tracheobronchial region = 4.901391
Percent deposited in pulmonary region = 14.6421
Extrathoracic deposition (percent) = 0

Mass (micrograms) deposited in airways during 8 hr:
Extrathoracic - 0.00
Tracheobronchial - 35.29
Pulmonary - 105.42

*** HUMAN MODEL
*** 0 % Nasal Breathing
*** Particle size (microns) = 1.4
*** Sigma G = 1.5
*** Tidal Volume (cm^3) = 1000
*** Respiratory Frequency = 12
*** Breath-holding pause (sec.) = 3
*** Aerosol Concentration = 15 mg/m^3
*** Date: 01-17-1991; Time: 17:04:00

Table 4

MS (EPA data, largerTV, lower resp.)

Mouth Breathing

Generation Number	Fractional Deposition	Surface Area	Surface Area at FRC	% of inhaled Aerosol deposited per cm^2	% of inhaled Aerosol deposited per cm^2 At FRC	Micrograms Deposited in 8 hr	Micrograms of Aerosol Deposited per FRC cm^2 in 8 hr.
1	2.174E-04	55.00	50.75	3.953E-04	4.284E-04	1.878E+01	3.701E-01
2	2.043E-03	33.44	31.12	6.109E-03	6.564E-03	1.765E+02	5.671E+00
3	2.113E-03	19.84	18.46	1.065E-02	1.145E-02	1.826E+02	9.893E+00
4	1.788E-03	11.62	11.14	1.538E-02	1.606E-02	1.545E+02	1.388E+01
5	1.970E-03	19.48	18.59	1.011E-02	1.060E-02	1.702E+02	9.154E+00
6	1.793E-03	42.34	39.65	4.236E-03	4.522E-03	1.549E+02	3.907E+00
7	1.750E-03	48.99	46.52	3.572E-03	3.761E-03	1.512E+02	3.250E+00
8	2.276E-03	103.75	97.27	2.193E-03	2.340E-03	1.966E+02	2.022E+00
9	2.744E-03	179.65	166.87	1.527E-03	1.644E-03	2.371E+02	1.421E+00
10	2.657E-03	196.87	184.68	1.349E-03	1.438E-03	2.295E+02	1.243E+00
11	3.512E-03	271.53	253.12	1.294E-03	1.388E-03	3.035E+02	1.199E+00
12	4.199E-03	346.84	323.04	1.211E-03	1.300E-03	3.628E+02	1.123E+00
13	4.905E-03	421.79	392.90	1.163E-03	1.248E-03	4.238E+02	1.079E+00
14	6.305E-03	506.99	472.01	1.244E-03	1.336E-03	5.447E+02	1.154E+00
15	7.093E-03	597.46	558.02	1.187E-03	1.271E-03	6.128E+02	1.098E+00
16	8.834E-03	804.67	756.21	1.098E-03	1.168E-03	7.632E+02	1.009E+00
17	8.845E-03	867.46	665.65	1.020E-03	1.329E-03	7.642E+02	1.148E+00
18	1.239E-02	1438.55	1113.50	8.612E-04	1.113E-03	1.070E+03	9.613E-01
19	1.612E-02	1977.53	1530.70	8.149E-04	1.053E-03	1.392E+03	9.096E-01
20	2.471E-02	3192.45	2471.11	7.740E-04	1.000E-03	2.135E+03	8.640E-01
21	3.918E-02	5241.18	4056.91	7.475E-04	9.658E-04	3.385E+03	8.344E-01
22	6.397E-02	9281.93	7184.65	6.892E-04	8.904E-04	5.527E+03	7.693E-01
23	9.630E-02	15561.79	12045.55	6.188E-04	7.995E-04	8.320E+03	6.907E-01
24	1.166E-01	35407.05	27406.72	3.292E-04	4.253E-04	1.007E+04	3.675E-01
25	0.000E+00	297311.40	490541.70	0.000E+00	0.000E+00	0.000E+00	0.000E+00

Percent deposited in tracheobronchial region = 5.419914
Percent deposited in pulmonary region = 37.80811
Extrathoracic deposition (percent) = 6.953334

Mass (micrograms) deposited in airways during 8 hr:
Extrathoracic - 6007.68
Tracheobronchial - 4682.81
Pulmonary - 32666.21

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References

1. Bailey, M.; Fry, F.; James, A. (1985): Long-term retention of particles in the human respiratory tract. J. Aerosol Sci. **16:**. 295-305.

2. Bangert-Downs, R.L. (1986): Review of developments in meta analytical methods. Psychology Bulletin **99:** 388-399.

3. Black, A. and Pritchard, J.N. (1984): A comparison of the regional deposition and short-term clearance of tar particulate material from cigarette smoke, with that of 2.5 μm polystyrene microspheres. J. Aerosol Science **15:** 224-227.

4. Bohning, D.; Atkins, H.; Cohn, S. (1982): Long-term particle clearance in man: normal and impaired. Ann. Occup. Hyg. **26:** 259-271.

5. Bond, J.A.; Sun, J.D.; Mitchell, C.E.; Dutcher, J.S.; Wolff, R.K. and McClellan, R.O. (1986): Biological fate of inhaled organic compounds associated with particulate matter. In: *Aerosols,* pp. 570-592. eds. Lee, Schneider, Grant, Verker. Lewis Publishers, Chelsea, MI.

6. Cohen, D.; Arai, S.F.; Brain, J.D. (1979): Smoking impairs long-term dust clearance from the lung. Science **204:** 514-517.

7. EPA: The Risk Assessment Guidelines of 1986. EPA/600/8-87/045 August 1987.

8. Gao, Y.; Blot, W.J.; Zheng, W.; Ershow, A.G.; Hsu, C.W.; Levin, L.I.; Zhang, R.; Fraumeni, J.F. (1987): Lung cancer among Chinese women. Int. J. Cancer **40:** 604-609.

9. Garfinkel, L. (1984): Passive smoking and cancer: American experience. Prev. Med. **13:** 691-697.

10. Grimmer, G.; Brune, H. ; Dettbarn, G.; Naujack, K.W.; Mohr, U. and Wetzel-Hartung, R. (1988): Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. Cancer Letters **43:** 173-177.

11. Hiller, F.; McCusker, K.; Mazumder, M.; Wilson, J.; Bone, R. (1982): Deposition of side stream cigarette smoke in the human respiratory tract. Am. Rev. Respir. Dis. **125:** 406-408.

12. Hirayama, T. (1981): Nonsmoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. British Med. J. **282:** 183-185.

13. Hinds, W.; First, M.W.; Huber, G.L.; Shea, J.W. (1983): A method for measuring respiratory deposition of cigarette smoke during smoking. Am. Ind. Hyg. Assoc. J. **44**(2):113-118.

14. IARC International Agency for Research on Cancer (1989): Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 46. Diesel and Gasoline Engine Exhaust and some Nitroarenes. IARC, Lyon.

15. Janerich, D.T.; Thompson, W.D.; Varela, L.R.; Greenwald, P.; Chorost, S.; Tucci, C.; Zamen, M.B.; Melamed, M.R.; Kiely, M. and McKneally, M.F., (1990): Lung cancer and exposure to tobacco smoke in the household. N. Engl. J. Med. **323:** 623-636.

16. Kilpatrick, S.J. (1980) Model specification effects in ETS/nutrition research. in: Kasuga, H. (ed): *Indoor Air Quality.* Springer-Verlag, Berlin, Heidelberg, pp. 256-271.

17. Kuller, L.H.; Garfinkel, L.; Correa, P.; Haley, N.; Hoffmann, D.; Preston-Martin, S.; Sandler, D. (1986): Contribution of passive smoking to respiratory cancer.; Environ. Hlth. Persp., **70:** 57-69.

18. Lee, P.S.; Gerrity, T.R.; Hass, F.J.; Lourenco, R.V. (1979): A model for tracheobronchial clearance of inhaled particles in man and a comparison with data. IEEE Trans. on biomed. Engin. Bme 26(11): 624-630.

19. Letzel, H. and Überla, K. (1980): Meta analysis on passive smoking and lung cancer. In: Kasuga, H. (ed) *Indoor Air Quality.* Springer Verlag, Heidelberg, pp. 316-322.

20. Martonen, T.; Hofmann, W. and Balásházy, I. (1989): Physical factors affecting lung deposition of cigarette smoke (with syncarcinogenic radon progeny effects) and mineral fibers. In: Wehner, A.P. and Felten, D.L. (eds): *Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke.* Battelle Press, Columbus, OH, pp. 159-181.

21. Muller, W.J.; Hess G.D.; Scherer, P.W. (1990): A model of cigarette smoke particle deposition. Am. Ind. Hyg. Assoc. J. **51**(5): 245-256.

22. NRC. National Research Council (1986): Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. National Academy Press, Washington, DC.

23. Schlesinger, R.B.; Lippmann, M. (1970): Selective particle deposition and bronchogenic carcinoma. Environ. Res. **15**: 424-431.

24. 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 exaust. Toxicol. Appl. Pharmacol. **73**: 48-59.

25. U.S. Surgeon General (1986): The Health Consequences of Involuntary Smoking. U.S. Dept. of Health and Human Services, Rockville, MD.

26. Wald, N.J.; Nanchahal, K.; Thompson, S.G. and Cuckle, H.S. (1986): Does breathing other peoples' tobacco smoke cause lung cancer? British Med. J. **293**:1217-1222.

27. Wolff, R.K.; Bond J.A.; Sun, J.D.; Henderson, R.F.; Harkema, J.R.; Griffith, W.C.; Mauderly, J.L.; McClellan, R.O. (1989): Effects of adsorbtion of benzo-a-byrene onto carbon black particles on levels of DNA adducts in lungs of rats exposed by inhalation. Tox. Appl. Pharma., **97**: 289-299.

28. Varela, L.R. (1987): Assessment of the association between passive smoking and lung cancer. Dissertation to Yale University for Ph.D. degree.

29. Vastag, E.; Matthys, H.; Zsamboki, G.; Kohler, D.; Daikeler, G. (1986): Mucociliary Clearance in Smokers. Eur. J. Respir. Dis. **69**: 107-113.

30. Yeh, M.; Schum H-C (1980): Theoretical evalutation of aerosol deposition in anatomical models of mammalian lung airways. Bull. Math. Biol., **42**: 1-5.

31. Yu, C.P.; Hu, J.P.; Yen, B.M.; Spektor, D.M.; Lippmann, M. (1986): Models for mucociliary particle clearance in lung airways. In: *Aerosols,* Ch. 39, pp. 569-578. Eds.: S.D. Lee, T. Schneider, L.D. Grant and P.J. Verkerk. Lewis Publishers, Chelsea, MI.