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EPA AN SAB REPORT: REVIEW OF DRAFT ENVIRONMENTAL TOBACCO SMOKE HEALTH EFFECTS DOCUMENT

REVIEW, BY THE INDOOR AIR QUALITY AND TOTAL HUMAN EXPOSURE COMMITTEE, OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S DRAFT REPORT: "HEALTH EFFECTS OF PASSIVE SMOKING: ASSESSMENT OF LUNG CANCER IN ADULTS AND RESPIRATORY DISORDERS IN CHILDREN" (EPA/600/6-90/006A)

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-IAQTHEC-91-007

April 19, 1991

OFFICE OF
THE ADMINISTRATOR

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
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Subject: Science Advisory Board's review of the Office of Research and Development document Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children, EPA/600/6-90/006A, June 1990, and the Office of Air and Radiation's draft document Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies, (EPA/400/6-90/004), June 1990.

Dear Mr. Reilly:

On November 1, 1990, the Offices of Research and Development and Air and Radiation requested that the Science Advisory Board (SAB) review the above referenced draft reports. The first document (hereafter referred to as the risk assessment report) incorporates a health risk assessment of the impact of passive smoking (i.e., exposure to environmental tobacco smoke, or ETS) on adult lung cancer incidence, and a discussion of the effects of exposure to ETS on the incidence and prevalence of respiratory disorders in children. The risk assessment report was prepared at the request of the Indoor Air Division, Office of Air and Radiation, to provide information and guidance on the potential hazards of indoor air pollutants. The second document (hereafter referred to as the policy guide) reflects and parallels the risk assessment report, but was not developed as a scientific document

The Agency sought the advice of the SAB's Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) concerning the risk assessment's accuracy and completeness, and the Committee's opinion on whether the weight of available evidence supported the conclusions drawn concerning ETS's roles in causing lung cancer in adults and respiratory disease in children. The SAB was also requested to review that portion of the policy guide which presented a scientific database on ETS.

The IAQTHEC met on December 4 and 5, 1990, in Arlington, Virginia to conduct its review of the ETS draft documents. In summary, the Committee found the risk assessment document to be a good faith effort to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, most of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the document to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, wherein it has been necessary to prepare and review two or more draft criteria documents prior to their endorsement by the Clean Air Scientific Advisory Committee. The IAQTHEC has suggested changes both in the organization and specific technical content of the draft, that if followed, can result in an improved ETS risk assessment document. The Committee also suggested changes that would strengthen the use of the incorporated scientific database to support the recommendations contained in the policy guide.

The Charge to the Committee, and associated findings of the Committee are outlined below:

A. Carcinogenicity Issues

1. Carcinogenicity of ETS Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in Category A, i.e., is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen, but notes that it had some difficulty in applying the Guidelines for Carcinogen Risk Assessment (51 FR 33992), as they are currently formulated, to this complex and variable mixture. We advise EPA to place greater weight on the biological considerations and the extensive experience with active human smoking to support the classification.

2. Spousal Smoking Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure. There are potential

important confounders related to spousal smoking status as a measure of exposure, but such confounding concerns are present in other surrogates of exposure as well.

3. United States and Foreign Studies Are the differences in relative risk observed between studies in the U.S. and those overseas of concern, and if so, to what degree?

The Committee believes that data from studies conducted in other countries, as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer, and does not find the observed differences to be of concern. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. Use of Meta-Analysis Is Meta-Analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

Meta-analysis is a general term applied to a wide range of techniques intended to synthesize findings across related studies. Although it is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, the emphasis given the meta-analysis of ETS/lung cancer association in this report is not justified. Biological considerations related to respiratory carcinogenesis and extrapolations from human exposure via active smoking provide compelling evidence that is consistent with the results of the meta-analysis.

5. Confounders/Misclassification Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as "never smokers") been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly, by carrying out a separate meta-analysis of those studies which included adjusted analyses. The potential main confounders included in these adjusted analyses were age and surrogates for confounding factors, including education, and social class. Comparison of relative risks in those studies which analyze both factors suggests that these effects are not important

confounders. As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust for them, since virtually none of the studies contains information on them.

6. Characterization of Uncertainties Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS (e.g. the carcinogenicity of ETS in some animal studies, and the presence of known human carcinogens in ETS); and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. These together appear to argue for a positive effect. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. Quantitative Risk Assessment Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulate matter as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data. This approach is direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens. Given that the epidemiology studies should be the basis of the risk assessment, some suggestions for refinements of the risk assessment are detailed in our report.

8. Home vs. Workplace Exposure Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and therefore on the relative impacts of home and workplace exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area.

B. Respiratory Disorders in Children

1. Weight of Evidence Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

The additional literature available since 1986 provides a basis for increased concern about the effects of ETS exposure on respiratory disorders. Thus, the Committee urges a thorough review of the entire body of evidence, including earlier reports covered in the 1986 reports of the Surgeon General and National Research Council. This review could be included in the revised risk document as Appendix E.

2. Confounders Have confounders in the epidemiologic studies been adequately addressed?

A number of confounders were mentioned by the report, but addressed improperly, including in utero exposure, parental reporting bias, and active smoking. One must stress both the biological precursors important to the effects of ETS in childhood, and the socioeconomic and behavioral factors.

3. Use of Meta-Analysis Should a meta-analytic approach be attempted as in the lung cancer analysis?

The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis.

C. Review of the Policy Guide

The Committee found, with some exceptions detailed in our report, that the scientific database incorporated in the policy guide is correct and appropriate. The policy guide should be revised to reflect changes made to the risk assessment report.

We appreciate the opportunity to review these issues, and stand ready to provide review comments on any significant revisions to the subject documents. We look forward to your response on the major points we have raised.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Morton Lippmann

Dr. Morton Lippmann, Chairman
Indoor Air Quality and Total
Human Exposure Committee

ENCLOSURE

ABSTRACT

The Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) met on December 4/5, 1990, to conduct its review of the environmental tobacco smoke (ETS) draft documents. In summary, the Committee found the risk assessment document to be a good faith effort to address complex and difficult issues affecting public health. Since the task is extremely difficult, it should come as no surprise that the Committee also found the document to be incomplete in many respects. The IAQTHEC has suggested changes both in the organization and specific technical content of the draft, that if followed, can result in an improved ETS risk assessment document. The Committee also suggested changes that would strengthen the use of the incorporated scientific database to support the recommendations contained in the policy guide.

The Charge to the Committee, and associated findings of the Committee are outlined below:

A. Lung Cancer in Adults

1. Carcinogenicity of ETS The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen.

2. Spousal Smoking Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure.

3. United States and Foreign Studies The Committee believes that data from studies conducted in other countries, as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer.

4. Use of Meta-Analysis It is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, but the emphasis given the meta-analysis of ETS/lung cancer association in this report is not justified.

5. Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the report. Comparison of relative risks (RRs) in those studies which analyze relevant factors suggests that these effects are not important.

6. Characterization of Uncertainties The draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high; and (2) the accumulating epidemiologic evidence on the relationship

between exposure to ETS and lung cancer. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. Quantitative Risk Assessment The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data.

8. Home vs. Workplace Exposure The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area.

B. Respiratory Disorders in Children

1. Weight of Evidence In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

2. Confounders A number of confounders were mentioned by the report, but addressed improperly, including *in utero* exposure, parental reporting bias, and active smoking.

3. Use of Meta-Analysis The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis.

C. Policy Guide The Committee found, with some exceptions detailed in the report, that the scientific database incorporated in the policy guide is correct and appropriate.

KEYWORDS: Environmental Tobacco Smoke (ETS); Carcinogenicity; Passive Smoking; Sidestream Smoke; Meta-analysis; Confounders; Lung Cancer; Respiratory Disease

U. S. ENVIRONMENTAL PROTECTION AGENCY

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U.S. Environmental Protection Agency
Science Advisory Board
Indoor Air Quality and Total Human Exposure Committee

Environmental Tobacco Smoke Review

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TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

The Committee's review of the environmental tobacco smoke (ETS) Risk Assessment document and Policy Guide found them to be good faith efforts to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, much of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the documents to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, where it has been necessary to prepare and review two or more draft documents prior to their endorsement by the Clean Air Scientific Advisory Committee (CASAC). This Committee has suggested both organizational and specific technical changes and additional analyses that, if followed, should result in improved ETS Risk Assessment and Policy Guide documents. The Committee stands ready to provide further review comments on the revised drafts.

The SAB was asked to address the following issues in reviewing the documents.

A. Lung Cancer in Adults

The Committee noted that Chapters 3 and 4 draft risk document addressed only the issue of lung cancer risk for non-smoking women due to spousal smoking. It is suggested that the revised document be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where considerable improvements could be made organizationally, and in terms of substantive content--particularly regarding material that was not adequately covered or not covered at all. We urge the EPA staff to redraft those chapters as well. Furthermore, we recommend the addition of a new chapter addressing addressing the physical, chemical, and dose considerations of ETS in relation to the same considerations for active smoking.

Findings on specific issues within the broader context of lung cancer in adults follow:

1. Carcinogenicity of ETS Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in

Category A, i.e., is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen, but notes that it had some difficulty in applying the Guidelines for Carcinogen Risk Assessment (51 FR 33992), as they are currently formulated, to this complex and variable mixture. The draft risk assessment document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS (e.g. the carcinogenicity of ETS in some animal studies, and the presence of known human carcinogens in ETS); and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. These together appear to argue for a positive effect. We advise EPA to place greater weight on the biological considerations and the extensive experience with active human smoking to support the classification.

2. Spousal Smoking Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure. The problems in not accounting for background exposure from other sources would, if anything, bias against finding increased risk of lung cancer. Bias related to misclassification associated with smoking status has been addressed and corrected for in this draft report. There are possible confounders related to spousal smoking status, but such confounding concerns are present in other surrogates of exposure as well. The potential importance of these confounders has been determined not to be sufficient to alter the conclusion that ETS increases the risk of lung cancer.

3. United States and Foreign Studies Are the differences in relative risk observed between studies in the U.S. and those overseas of concern, and if so, to what degree?

The Committee believes that data from studies conducted in other countries, as well as in the United States, should be

utilized in evaluating whether exposure to ETS increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. Use of Meta-Analysis Is Meta-Analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

Meta-analysis is a general term applied to a wide range of techniques whose objective is to synthesize findings across related studies. Although, it is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, the emphasis given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Biological considerations related to respiratory carcinogenesis (e.g., biologic plausibility) are equally compelling. Given the similarities in composition between mainstream smoke and ETS, biological considerations related to respiratory carcinogenesis and the extensive evidence on active smoking should receive greater weight.

5. Confounders/Misclassification Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as "never smokers") been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The potential main confounders included in these adjusted analyses were age and surrogates for confounding factors, including education, and social class. Comparison of unadjusted and adjusted relative risks (RRs) in those studies which present both factors suggests that these effects are not important confounders.

As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust

for them, since virtually none of the studies contains information on them.

The issue of misclassification should not be restricted to misclassification of current smokers and ex-smokers as "never smokers." It should also be mentioned that misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

Not enough attention was given to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null.

6. Characterization of Uncertainties Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon the two main arguments noted earlier: (1) the biological plausibility of such a causal association; and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. With exposure levels that are usually quite low, it is not surprising that the association is likely to be weak although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

Epidemiologic evidence on the relationship between exposure to ETS and lung cancer should be described more completely, with the deficiencies of individual studies used to weight their contributions to any conclusions that are drawn. The assumptions and uncertainties associated with each step of the risk assessment process ought to be explicitly stated.

7. **Quantitative Risk Assessment** Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulate matter as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data. This approach is direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended with respect to:

1. Criteria for Including Individual Studies in the Meta Analysis
2. Adjustment for Smoker Misclassification
3. Misclassification of Exposure
4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking
5. Dose-Response Estimation of Risk

8. **Home vs. Workplace Exposure** Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and therefore on the relative impacts of home and workplace exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area. The report should also review and comment on the data that exist on exposure to ETS in public places.

B. Respiratory Disorders in Children

Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantially improved and that the conclusions drawn in it could be made much stronger if the chapter were revised in the manner suggested in this report.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than that stated in Chapter 5 of the draft ETS Risk Assessment document, and recommends that the new draft contain a more comprehensive discussion on quantitative risk assessment for these effects.

Specific issues are addressed below:

1. Weight of Evidence Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

The additional literature available since 1986 provides a basis for increased concern about the effects of ETS exposure on respiratory disorders. Thus, the Committee urges a thorough review of the entire body of evidence, including earlier reports covered in the 1986 reports of the Surgeon General and National Research Council, and its incoporation as Appendix E.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

2. Confounders Have confounders in the epidemiologic studies been adequately addressed?

A number of confounders were mentioned by the report, but addressed improperly. These include in utero exposure, parental

reporting bias, and active smoking. One must also stress both the biological precursors important to the effects of ETS in childhood, and socio-economic and behavioral factors.

3. **Use of Meta-Analysis** Should a meta-analytic approach be attempted as in the lung cancer analysis?

The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined for meta-analysis for lung cancer.

The Committee was also asked to examine whether the draft Policy Guide's statements on health contained within the first 20 pages were scientifically defensible. With some exceptions, detailed in the this report (section 4.0), the scientific data and interpretations contained in the draft Policy Guide were appropriate. The Policy Guide draft will need to be revised to reflect the changes being made in the Risk Assessment.

2.0 INTRODUCTION

2.1 Background On November 1, 1990, the Offices of Research and Development and Air and Radiation requested that the Science Advisory Board (SAB) review the draft report "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," which incorporated a health risk assessment of the impact of passive smoking on lung cancer incidence. The document was prepared by the Human Health Assessment Group, Office of Research and Development, at the request of the Indoor Air Division, Office of Air and Radiation, under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

The draft risk report reviews and analyzes the data on the respiratory effects of environmental tobacco smoke (ETS) with heavy emphasis on the epidemiologic data and statistical (meta) analysis. One major portion of the Report (Chapters 3 and 4) examines the weight of evidence for lung cancer in adults. It concludes that under EPA's carcinogen assessment guidelines, ETS should be classified as a Category A or known human carcinogen.

It also estimates from epidemiology (not modeling) data that, on average, 3,800 lung cancer deaths per year in U.S. nonsmokers are attributable to ETS. The final chapter of the report examines the epidemiological evidence for non-cancer respiratory disorders in children and concludes that the detrimental respiratory effects described are associated with exposure to ETS, but that a causal association has not been established.

The draft report also contains four appendices. Appendix A provides a detailed summary and analysis of eleven recent case-control studies of ETS and lung cancer. Appendix B presents pertinent mathematical formulae and relationships. Appendix C describes the dosimetry of ETS, and Appendix D presents a potential framework for dose-response modeling for ETS and lung cancer.

The draft risk report was made available for public review and comment on June 25, 1990, with a 90-day comment period which closed Oct. 1, 1990. Over 3,500 copies were distributed and 107 public comments were received as of Oct 10, 1990. A summary of those comments were prepared and provided to the SAB Committee.

2.2 **Scope of Issues/Charge to the Committee** The Agency sought the advice of the SAB on the draft risk document's accuracy and completeness. The Agency also wanted an opinion on whether the weight of available evidence supported the conclusions drawn concerning ETS's role in causing lung cancer and respiratory disease. In addition, the SAB was asked to address the following specific issues:

A. Lung Cancer in Adults

1. Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in Category A, i.e. is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

2. Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

3. Are the differences in relative risk observed between studies in the U.S. and those overseas of concern, and if so, to what degree?

4. Is meta-analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

5. Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as never smokers) been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

6. Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

7. Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulates as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

8. Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

B. Respiratory Disorders in Children

1. Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

2. Have confounders in the epidemiologic studies been adequately addressed?

3. Should a meta-analysis approach be attempted as in the lung cancer analysis?

The SAB was also asked to comment on the scientific foundations of a second draft document, "Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies," (hereafter refered to as the "Policy Guide") produced by the Indoor Air Division of the Office of Air and Radiation.

2.3 Conduct of The Review The review was assigned to the SAB's Indoor Air Quality and Total Human Exposure Committee. The Committee met on December 4 and 5, 1990 in Arlington, Virginia to receive briefings from EPA staff, hear extensive comments from members of the public, and discuss the several issues embodied in the charge. Following the discussions, the Chair requested that designated Members of the Committee provide written materials organized to respond to the charge, and reflecting the preceding interactions. Those materials, after editing and review by all Members of the Committee constitute this report.

3.0 REVIEW OF THE RISK ASSESSMENT DOCUMENT

The preparation of a risk assessment document for ETS represents a formidable challenge, and the Committee recognizes the quite considerable efforts put forth by EPA staff in preparing the draft. The document contains some excellent summary materials on a large and diverse set of relevant literature, as well as some skillful and pertinent analyses that serve to address the critical issues related to the public health impact of exposures to ETS. Although we commend EPA for its efforts, we find that the document could be substantially improved, and recommend a series of specific changes in organization and content that, if followed, would make the revised document a much stronger basis for policy guidance on ETS exposure and its health effects. Since the impact of ETS on public health is comparable to that of some of the criteria air pollutants, we recommend that the revised document follow more closely the format of the Air Quality Criteria Documents. It should include additional chapters addressing the physics and chemistry of ETS, its relation to mainstream smoke, the exposures of various populations of interest to ETS, and as appropriate to the discussions of biological plausibility and weight of evidence, those aspects of dosimetry which will be needed to support other parts of the document. The contents of these additional chapters should strengthen the basis for any actions or recommendations.

The Committee also reviewed the utility, format and adequacy of the five appendices to the ETS Risk Assessment Document. We found them to be of varying utility and quality, and made specific suggestions for revisions and deletions.

3.1 Chapter 3--Epidemiologic Evidence of Lung Cancer from ETS The focus of this chapter is on hazard identification: that is, determining if the available evidence on ETS warrants the conclusion that exposure to ETS increases the incidence of lung cancer. As described in the Agency's "Guidelines for Carcinogen Risk Assessment," hazard identification is a qualitative process that involves review "...of the relevant biological and chemical information bearing on whether or not an agent may pose a carcinogenic hazard." The scope of hazard identification is broad, involving review of information on 1) physical-chemical properties and routes and patterns of exposure; 2) structure-activity relationships; 3)

metabolic and pharmacokinetic properties; 4) toxicologic effects; 5) short-term tests; 6) long-term animal studies; and 7) human studies.

The present chapter, comprising the hazard identification step of the risk assessment, seems limited in scope when measured against the encompassing process set out by the Agency. Although the appendixes do address exposure and toxicology to an extent, this material needs more direct discussion in the chapter. The components of ETS possibly relevant to this risk assessment should be reviewed along with the characteristics of mainstream and sidestream smoke, and similarities in composition and from in vitro bioassay should be discussed. The complexity of ETS merits emphasis; it is not a single chemical agent, but a mixture with varying characteristics by place and time in relation to its formation in the burning cigarette. The toxicologic effects of individual components merit further discussion. Exhaustive review is not needed, since the Surgeon General's Reports provide comprehensive documentation.

In reviewing the human evidence, the chapter fails to draw on the voluminous evidence on active smoking and lung cancer. The 1986 Surgeon General's Report, for example, concluded that there was enough toxicologic similarity between mainstream smoke and ETS to justify using the evidence from active smoking in reaching conclusions concerning ETS and lung cancer. The evidence on active smoking and lung cancer documents the consequences of a higher level of exposure to a mixture, mainstream smoke, that resembles ETS in composition. The epidemiologic evidence on ETS and lung cancer in nonsmokers should be considered as addressing the risks of lower levels of exposure. Thus, the evidence on active smoking and lung cancer needs to be reviewed in this chapter. The causal nature of the association between active smoking and lung cancer should be described, as should exposure-response relations for active smoking and lung cancer. The Surgeon General's Reports could serve as the basis for developing this material.

The existing chapter reviews case-control and cohort studies providing information on the association of ETS with lung cancer. Characteristics of these studies are considered. Several statistical approaches are used to assess the aggregate significance of the evidence and a pooled relative risk estimate with associated confidence limits is calculated. The chapter concludes with a

review of potential biases affecting interpretation of these studies, with an emphasis on misclassification.

The roster of studies selected represents those available through the time at which this draft report was released; in revising the draft, consideration should be given to substituting the data from the recent report by Janerich et al. (1990) for the earlier analysis of these same data (Varela, 1987). The features of the individual studies are adequately reviewed.

The discussion of bias (Section 3.5) needs expansion and some consideration of types of bias other than misclassification. The types of bias potentially affecting any epidemiological study include selection bias, information bias (which includes both differential and non-differential misclassification), and confounding bias. Selection bias, particularly likely to affect case-control studies based on cases and controls derived from specific institutions, should be addressed. The possibility of confounding bias merits review because of evidence that smokers are increasingly distinct from nonsmokers in socioeconomic characteristics that may have implications for health. Thus, those more highly exposed to ETS may differ from those less exposed in other relevant characteristics. Confounding, however, is an unsatisfactory explanation for the general pattern of the reported studies, with the majority showing increased risk. These studies have been conducted in a wide variety of locales with consistent findings of positive association; this consistency weighs against confounding as an explanation for the increased risk associated with marriage to a smoker. The discussion of misclassification should be expanded to include studies that have addressed the quality of information on passive smoking derived from questionnaires as well as the relation between questionnaire-based measures of exposure and biological markers of exposure. The 1990 Report of the Surgeon General includes reviews of the quality of information on smoking from surrogate respondents as well as of the validity of self-report of smoking history; this recent report should be considered and cited in the discussion of misclassification.

Two major cohort studies providing evidence on passive smoking and lung cancer have been published; a lengthy discussion is provided concerning the comparative findings of the two studies. Unfortunately, we lack information on the comparative exposures to ETS of subjects in the two populations. For both studies, follow-

up periods began well before present methods for atmospheric monitoring or for assessing biological markers were available. Thus, arguments concerning the possibility that passive smoking is more "direct" in Japan are speculative and the lack of data should be cited and uncertainty added in drawing any conclusion concerning the comparative levels of exposure in the U.S. and Japan. The discussion of the two studies should be markedly shortened.

In summary, Chapter 3 of the May 1990 External Review Draft provides a generally adequate review and assessment of the epidemiologic evidence on ETS and lung cancer in never smokers. A complete hazard identification is not conducted, however. The chapter needs to be expanded to address more fully the toxicology of ETS and the evidence on active smoking and lung cancer. This expanded review, coupling more closely the evidence on biological plausibility that ETS is a carcinogen with the supporting epidemiological evidence would adequately support the conclusion that ETS is a Group A carcinogen, a determination that should be moved from the quantitative risk assessment (current Chapter 4) to Chapter 3. The Committee accepts this overall conclusion, in spite of the limitations of the current chapter; a more comprehensive review as suggested by the Committee should strengthen the determination that ETS is a Group A carcinogen.

3.2 <u>Chapter 4--Assessment of Lung Cancer Risk from ETS</u> In reviewing published quantitative risk assessments, Chapter 4 of the review draft properly dichotomizes the approaches that have been taken -- the cigarette-equivalent approach, and analyses of epidemiologic studies in which the excess lung cancer risk in non-smokers is observed as a function of exposure to ETS. As indicated in Chapter 4, there are serious difficulties in both of these approaches. The cigarette-equivalent approach has the great advantage that it is based on relatively abundant and consistent relative risk (RR) determinations in active smokers, which can be used to project the risk in non-smokers exposed to ETS in the form of a percentage of the risk in active smokers.

The assessment of the cigarette-equivalent in non-smokers due to exposure to ETS has a considerable level of uncertainty embedded in it. The ratio of sidestream (SS) to mainstream (MS) emissions is highly variable among the components of cigarette smoke, so that the number of cigarette-equivalents to which a passive smoker is exposed varies greatly with the compound used as a marker or expo-

sure surrogate. Neither cotinine concentration in body fluids nor the measurement of tobacco smoke particulate matter can be used with great confidence for quantitative assessment of the carcinogenic potential of ETS. There is a suggestion that the uncertainty in exposure assessment for either approach is about an order of magnitude (It should be noted here that the Guideline for Carcinogenic Risk Assessment anticipates that numerical risk estimates will have no more than one significant digit). Neither cotinine nor smoke particulate matter levels are direct indicators of carcinogenic components.

The other type of assessment is based on inferences from the epidemiologic studies of the association of exposure to ETS and carcinogenic risk in non-smokers. Since spousal smoking is a very important exposure proxy used in many studies, the utility of a categorical classification (married to a smoker/not married to a smoker) for quantitative exposure assessments needs to considered. Physical proximity of smokers to non-smokers), daily length of exposure, and exposure outside the home to ETS may be quite different in different cultures and over decades of time. Misreporting of smoking status for cases and controls in these studies may also introduce a bias. Various attempts have been made to apply corrections for these sources of bias. These attempts require further assumptions and are based on limited data available on misreporting rates and cotinine concentrations in various groups.

The assessment presented in the last section in Chapter 4 of the Review Draft does not appear to be in conflict with procedures established in other reviews, and states all assumptions made in the quantitative assessment with considerable care. The results are given in too many significant figures however.

3.3 <u>Chapter 5--Environmental Tobacco Smoke and Respiratory Disorders in Children</u> The Committee recommends that this chapter be re-organized to reflect directly the biological effects of Passive/Involuntary smoking (This terminology reverts to the original discussion of exposure-response and its impact, as per the Surgeon General reports of 1982-1986). The chapter should treat <u>in utero</u> exposure as a precursor to extra uterine/post birth/childhood effects, and not as a confounder. It should also be extended to address effects in adults, since the sequelae of effects in chil-

dren, as well as direct effects in adults, naturally proceed from the discussion of effects in children.

The Committee's recommendations as to the structure for a revised chapter follow. In outline, the proposed sections would be: an Introduction; 1) Biological Mechanisms; 2) Exposure and its Assessment; 3) Annoyance and Irritation; 4) Acute Illnesses (middle ear, upper respiratory, lower respiratory); 5) Chronic Respiratory Systems and exacerbations of chronic obstructive pulmonary disease (COPD); 6) Asthma; 7) Pulmonary Function; and 8) Health Hazard Assessment.

The Introduction of the Chapter should include some reference to the overall problem of acute and chronic respiratory diseases, and the potential attributable risk of ETS/passive smoking (Chronic respiratory disease is the fifth leading cause of death, with an age-adjusted death rate of $15.7/10^5$ in 1985; it is increasing still. Acute lower respiratory disease is the sixth leading cause of death, with an age-adjusted death rate of $13.4/10^5$ in 1985. The prevalence rates of related conditions are significant--the rate for asthma, for example, is $4.1/10^2$ (NCHS, 1986). Acute respiratory disease is the leading cause of morbidity and disability in the U. S. (as per NCHS)).

The first section of the Chapter could be called Biological Mechanisms (5.1). It should discuss the biological plausibility of the respiratory responses (akin to the discussion of carcinogenicity), and a brief discussion of the comparable response to active smoking. Such topics as irritant responses to pollutants (as are found in ETS) have been discussed at length in EPA Office of Research and Development and Office of Air Quality Planning and Standards (OAQPS) documents (e.g., National Ambient Air Quality Standards (NAAQS) Criteria Documents and Staff Papers, and National Emissions Standards for Hazardous Air Pollutants (NESHAP) Criteria Documents.

It should start with the effects of in utero exposure effects as precursors to childhood effects (5.1.2.): reduced fetal oxygenation, poorer lung (and brain) development, low birth weight, immunological and biochemical effects (e.g., changes in T cells and immunoglobulin levels, changes in prostaglandin regulation, pro-

tease inhibitors) (Amer. Acad. Peds. J. Peds., 1976; ALK report, 1983; Wall et al., 1985; Rantakallio, 1978; McIntosh, 1984; Tager, 1988).

The next discussion (5.1.3) could be of the effects of low lung function at birth (due to genetics and in utero exposure) as a precursor of lower respiratory infections; poorer lung development (disposing to greater effects of ETS on lung growths) (Martinez et al., 1989; Sherrill et al., 1990; Lebowitz, 1991), as discussed at the Committee's meeting).

There should be a discussion (5.1.4) of the potential reduction in host defense mechanisms due to ETS (going further than that induced by in utero passive smoking), which is of a similar nature (though a different dose) to that induced by active smoking. This topic relates to the increased predisposition to and prevalence rates of acute illnesses (middle ear, upper respiratory, lower respiratory, other exacerbations of chronic respiratory disease/chronic obstructive pulmonary disorder/airway obstructive disease (COPD/AOD)).

The next logical discussion (Section 5.1.5) could concern how these experiences could lead to chronic respiratory disease (e.g., chronic cough, persistent wheeze) in childhood, and how the sequelae of such would be chronic respiratory disease in adult life. The pathophysiological and anatomical mechanisms would be featured, and some discussion of biochemical mediators would occur.

There should be a discussion (5.1.6) of the biological reasons why ETS would produce or exacerbate bronchial lability and responsiveness (BR) (coupled to the lower airway caliber, and possibly genetics, discussed above), and how this BR, especially in conjunction with increased Immunoglobulin E and lower respiratory infections (both discussed above) could lead to childhood wheezy bronchitis and asthma (Tager, ARRD, '88; 138:507; Burrows and Martinez, ARRD, '89 140:1515). The role of atopy (also genetically regulated) in this process should be discussed (ibid.).

The role of these above-mentioned conditions (BR, bronchitis, asthma/persistent wheeze) on decreased lung growth (Sherrill, op cit.) should be discussed. This could lead into a general discussion (5.1.7.) of why lower lung function is related pathophysiologically to ETS, starting with deceased lung growth in

utero (see above), and how this would lead to low lung function/COPD in adults (Tager et al., 1987; Lebowitz et al., 1987). Appropriate biochemical and anatomic mechanisms would be discussed.

Unless the relevant material is covered generically in an earlier chapter, Exposure and its Assessment could be covered in a seperate second section (5.2). Such a section would cover reported exposures, measurements of indoor nicotine, other related pollutants (PM, CO, etc.), and biological markers such as cotinine (Jarvis et al., 1987). Factors associated with ETS (cf., Sandler et al., 1989) should be presented as relevant. Other methods of exposure estimation and assessment should also be discussed, including utilization of models based on source characterization from chamber studies. The relationships between reported exposures and monitoring results, and biases in reporting (cf., Friedman et al., 1983) could be discussed also. Confounding needs to be discussed (Quackenboss et al., 1989; Lebowitz, 1990) as well (other key references include National Research Council (NRC) 1981; World Health Organization (WHO) 1982; NRC 1986, and WHO/EURO Proceedings on Indoor Air 1984, 1987, and 1990.) Further, exposure-dose estimation would be presented (Hiller et al., 1982).

The third section (5.3) should address Annoyance and Irritation. Annoyance is important per se, and annoyance also affects subjective reports (Lebowitz, 1989; Department of Health, Education, and Welfare 1971; National Institute of Occupational Safety and Health 1971; National Clearinghouse on Smoking and Health 1976; NRC 1981, Surgeon General's Report 1986) (Odor topics should be included in this section, introducing the concept of sensitive individuals). Irritation effects are well-documented (Weber, and Hugod, 1984), and occur more quickly at lower doses in those more "sensitive" (ibid., op cit). Acute irritant symptoms should be a major topic. This section should document such effects in children and adults, and differentiate irritant from infectious and allergenic effects.

The fourth section (5.4) should cover Acute Illnesses. This includes middle ear effusions (5.4.1), upper and lower respiratory illnesses (including such exacerbations of COPD) (5.4.2-.4), and sequelae of lower respiratory illnesses. The effects of LRI's on lung function (e.g., Yarnell and St. Leger 1979), and the possibility of LRI's leading to asthma in children (Gregg, 1973) war-

rants discussion. The effects of LRIs leading to asthma in children (Gregg, 1973) should also be discussed. The effects of LRIs also includes AOD in adults (the overall effects of childhood respiratory troubles (CRT)), especially as documented in longitudinal studies (Lebowitz et al. 1987, 1988; and Sherrill et al. 1990); this could be a separate section (5.4.6).

Airway obstructive disease should be addressed in a major section because of the well-documented effects of ETS on lower respiratory tract illnesses, and the above-mentioned sequelae. The EPA report did a reasonable job in this area, and can be expanded (by incorporating some of the comments included in the reviews by Samet and Lebowitz). Further discussion of biases in reporting are available (Colley 1974; Cederlof and Colley 1974), as well as for confounding by other exposures (Hammer et al. 1976; Anderson, 1979; Speizer et al. 1980; Comstock et al., 1981; Melia et al. 1982; Koo et al. 1988), and interactions with other exposures (Lebowitz et al. 1989 and 1990). There should also be discussion of the concurrent effects of breast feeding and socio-economic status (Martinez et al., '89, '90).

The <u>fifth section</u> should cover <u>Chronic Respiratory Symptoms</u> (and increases of symptomatology in COPD as exacerbations). Some of this topic was covered in the EPA report, but it could be improved by clarification and expansion (see reviews provided). Again, biases in reporting, confounding by other exposures, and interactions of exposures producing responses (ibid., op cit.) warrant discussion. Effects of active/self-smoking interacting with passive smoking should be discussed (Bland et al., 1978; Lebowitz et al. 1987 and 1988). Effects of family history (ibid., Schilling et al. 1977; Weiss et al. 1980) should also be covered. Sequelae (op cit.) could be discussed as well, and direct effects in adults also (Comstock et al. and Schilling et al., ibid.; Lebowitz and Burrows, 1976; Schwartz and Zeger, 1990).

The <u>sixth section</u> (5.6) should cover all the aspects of <u>Asthma</u>. This section is one of the most important, and was one that was insufficiently discussed (in all aspects) in the EPA report. It needs to discuss genetic and <u>in utero</u> aspects, the evidence for bronchial responsiveness, high IgE and atopy related to ETS (Weiss et al. 1983 and 1988; Tager 1988; Burrows & Martinez 1989; and Lebowitz et al. 1989 and 1990, op cit.). The effects of social status, breast feeding, other exposures, and sequelae should

be discussed as well (op cit.; Rantakallio 1979; Sherman et al., 1990). Other studies, in press, could also be used (e.g., Martinez et al., Peds.). Exacerbations can be studied as well, including those seen in field studies (Quackenboss et al. and Lebowitz et al. 1989-1991, op cit.) and chamber studies (Shephard et al. 1979; Dahms et al. 1981; Stankus et al. 1988; Danuzer et al. 1991).

The seventh section (5.7) should cover effects on Pulmonary Function alluded to above, in the EPA report, including all the previous effects (and confounders, etc.) discussed above. It should be more precise, and include amount of change found.

There could be a section at this point covering other, miscellaneous topics, as in the previous report. Alternatively, these topics could be put into other sections.

The eighth section (5.8) would be a Health Hazard Assessment, which would include attributable risk and population impact. Further discussion is needed concerning the initial aspects of the section.

3.4 Appendix A--Summary Descriptions of Eleven Case-Control Studies The Committee agreed that Appendix A made a valuable contribution to the document, and that it should be included in the final draft. Much of the information contained in the appendix might be more useful however, if it was organized as a series of tables rather than a running text description. For example, a table that described the important characteristics of the study, e.g., population size, number of lung cancers, measure of ETS exposure used, characteristics of the control population and criteria for selecting the cases. Other tables might include potential biases addressed or not addressed in each of the studies and smoking characteristics in the background and control populations.

3.5 Appendix B--Mathematical Formulas and Relationships The Committee agreed that Appendix B is important to the overall report. However, in its present form, it contains several errors, both typographical and substantive, which should be corrected. Moreover, its format is difficult to read, and it is incomplete. The Committee recommends that Appendix B be restructured and rewritten in a more "reader friendly" style to include, as a minimum, the following three sections:

1. An Introduction to describe the purpose of the Appendix and its objectives.

2. An overview of the Mantel-Haenszel procedure that was used in this report for the meta-analysis. This section should also include a rationale for the selection of this procedure, rather than the method used in the previous NRC report. Appendix B in the NRC report is suggested as a guide for the presentation of this material.

3. Description and derivations of the risk assessment equations used. A rationale for the specific equations, a discussion of the validity of these equations for case-control as well as cohort studies, and explicit assumptions pertaining to the equations should be included in this section. The Committee also suggests that the derivations be presented in a systematic format for ease of reader understanding:

   a. A new section on the derivation of the unadjusted relative risk equation. (This could be incorporated with item 2, above).

   b. A revised section on the derivation of the relative risk equation adjusted for misclassification (B1).

   c. A revised section on the derivation of the relative risk equation adjusted for background exposure (B2).

   d. A revised section on the derivation of the equation to estimate the population-attributable risk (B3).

Specific written comments pertaining to Appendix B were submitted by several Committee members. These comments identified several errors, typographical and substantial, in the equations. The Committee therefore recommends that these errors be corrected and that the results based on these equations be carefully reviewed before final publication. For example, it was acknowledged at the Committee meeting in December that the correction of one such error resulted in a slight downward shift of the predicted annual lung cancer deaths due to passive smoking.

3.6 Appendix C--Dosimetry of ETS The Committee agreed with EPA staff that Appendix C should be deleted in its present form. Some of the issues that are addressed in Appendix C should be addressed in at least one or more of the new chapters, but in a format appropriate to a chapter, rather than a format considered appropriate to an appendix.

When incorporating the discussion now located in Appendix C into appropriate text chapters, it should be noted that the Appendix, as written, has serious technical errors and limitations. It is seriously deficient in that it focusses entirely on carcinogens and their dosimetry in healthy adults. This is inadequate even when the endpoint of concern is lung cancer, as evidenced in the recent report of Janerich et al. (op. cit.) on the association between lung cancer in adults and their childhood exposure to ETS. It is even more inadequate in that it ignores the respiratory disorders in children that are reviewed in great detail in Chapter Five.

The whole section C-5, "INTERNAL ORGAN BURDENS FOR THE LUNG," is based upon a simplistic set of models and assumptions that produce regional lung retention times and dose estimates that are truly fanciful. It correctly states "that removal from the tracheo-bronchial region generally may be characterized by two phases. The first is a rapidly cleared phase, dominated by particles deposited on the mucus of the upper passageways. The second is dominated by particles deposited on the slowly moving mucus of distal passageways." However, the calculated half-times (C_1 and C_2) of 450 and 710 minutes, respectively, for the fast and slow phases of ETS particle clearance, differ considerably from the actual radio-aerosol study data on which the model is supposedly based, and which show much faster rates.

The literature on the effect of active smoking on particle deposition and clearance rates is misinterpreted. One study of Albert et al. (1975) concerning the short-term effects of smoking on overall tracheobronchial clearance in humans, and one study by Wanner et al. (1973) on the effects of chronic smoke exposure on mucociliary transport velocity in the trachea of the dog are cited as a basis for doubling the retention times of particles on the tracheobronchial tree as a whole. The conclusion was drawn that smoking has no effect on the regional deposition of particles. The reality is quite different. Smokers have much greater tracheo-

bronchial deposition than nonsmokers, and the short-term effect of smoking is to greatly accelerate the clearance of particles deposited on the tracheobronchial tree. It is curious to note that the C_2 value calculated for the second "fast-phase" component in smokers is 1400 min (23.3 hours), while a 17 hour half-time was used for the "slower" alveolar region half-time in the dose calculations.

3.7 **Appendix D--Alternative Approaches for Estimating the Yearly Number of Lung Cancer Deaths in Non-Smokers Due to ETS Based on Dose-Response Modeling** The major purpose of Appendix D is to bolster the risk assessment document. Much of the data referenced in this appendix provide further evidence of the carcinogenicity of environmental tobacco smoke, and should be clearly presented in this light. For instance, the Grimmer study clearly demonstrates the lung carcinogenicity of ETS in animals. Other sections are currently incomplete and point to future directions for research. While interesting, these sections are not as supportive of the main document and may be distracting.

The first two approaches for deriving ETS dose-response models, the relative potency approach and the cigarette equivalent approach, share an implicit assumption that particle phase compounds, and polynuclear aromatic hydrocarbons in particular, are the carcinogens of interest. Other carcinogens have been identified in ETS, and many of these are in the vapor phase, e.g., benzene, vinyl chloride, formaldehyde, and several N-nitrosamines. To the degree that vapor phase carcinogens have been ignored, or incompletely collected or extracted for administration in animal experiments, the potency of ETS has been underestimated. Furthermore, the use of benzo-[a]-pyrene as a reference standard of human lung cancer is highly problematic and should be reconsidered.

The uncertainties in the relative potency approach are too great to support the derivation of an ETS dose-response model that would be an improvement over any that can be calculated from epidemiologic data. The relative potency in animals is not necessarily the same as the relative potency in humans, especially to the degree that metabolism may be involved. Furthermore, the data do not exist to support calculating the relative potency by a straightforward comparison, e.g., ETS and compound X in animal system A, compared with a known dose-response relationship for compound X in humans, so other intermediate comparisons are re-

quired, such as compound X and mixture Y with different routes of exposure, on different animals, and with different tumors. The uncertainties of each step quickly overwhelm the uncertainties in the epidemiologic studies.

The complexities of tobacco emissions complicate the cigarette equivalent approach. The referent mainstream emissions should be those of unfiltered cigarettes, upon which most of the active smoking epidemiologic data is based. The variable ratios in sidestream to mainstream emissions of toxins lead to differences in the calculated cigarette equivalents to which a passive smoker is exposed, and these may range over two orders of magnitude (see Hammond, 1990). These different emission ratios are a source of variability in the ratio of biomarkers in smokers and nonsmokers. (Metabolism rates are another potential difference.) Thus, cotinine in nonsmokers is typically less than 1% the level found in smokers, while the median level of 4-aminobiphenyl hemoglobin adducts in nonsmokers was 14% the median in smokers (Hammond et al, 1990). This corresponds to the emission ratios of these compounds, which differ by a factor of 15. Russell and coworkers (1986) (page 4-19) based their estimates of the risk of premature death from passive smoking on the ratio of cotinine in passive smokers to that in active smokers, 0.007, and assumed the same ratio held between premature deaths in passive and active smokers. The use of 4-aminobiphenyl hemoglobin adducts instead of cotinine to estimate relative exposures would have led to a higher predicted premature death rate due to passive smoking.

Several studies have been conducted on the deposition of MS and SS particles in the human lung. These should be discussed rather than relying solely on biomarkers, where the exposures are not known. A few caveats are required regarding the use of DNA adducts to estimate dose. DNA adducts are subject to repair mechanisms, and the rate of repair may differ in smokers and nonsmokers. Since nonsmokers have very different exposures to ETS, one expects a wide range in the ratio of adducts in smokers and nonsmokers. A disadvantage in the exclusive use of DNA and protein adducts as biomarkers of dose is that such markers are available for only a few suspected agents. The use of benzo[a]pyrene (BaP) DNA adducts is further complicated by the many other sources of BaP, including diet and various combustion products.

Determination of the dose-response effect of ETS based on the epidemiologic studies of Hirayama would be most valuable. The data gathered by Hirayama and colleagues could have been greatly enhanced and more generalizable if measurements of ETS levels (especially respirable particle and nicotine concentrations) had been taken in Japanese homes with varying amounts of smoking.

Some of the methods used in Appendix D might be useful in estimating the importance of ETS in respiratory diseases in children. Appendix D has information which is supportive of the main document. Some of this information can be improved; some is suggestive of future research directions. The release of the final document should not be delayed for these data. Finally, the data may be best incorporated into the relevant sections of the main document, rather than exist as an independent appendix.

3.8 Appendix E--Summary Descriptions of Twenty-Six Studies on Environmental Tobacco Smoke and Respiratory Disorders in Children

The Committee concluded that an Appendix E, similar to the Appendix A, should be included in the revised document. As before, the Committee recommends that the information by organized as a series of tables rather than as a running text description with a similar format.

4.0 REVIEW OF THE POLICY GUIDE

The Policy Guide was not prepared as a scientific document, but its recommendations are based upon summary statements of scientific knowledge. On this basis the Committee was agreed to examine whether the Guide's statements on health contained within the first 20 pages were scientifically defensible. The Committee did note that there is much technical content in other sections of the Policy Guide, including technical statements on ventilation, room and building ventilation.

For the most part, the scientific data and interpretations contained in the draft Policy Guide were appropriate, but there were some notable exceptions -- an incorrect definition as to what constitutes a small particle, an erroneous statement as to the depth of penetration of mainstream smoke vs. sidestream smoke, and a misstatement of the current particulate matter NAAQS, to cite a few. Furthermore, there were statements about cardiovascular mortality, cancers at other sites, and aggravation of cardiovascular and respiratory disease that were not addressed in the ETS Risk Assessment. Thus, without having any supporting documentation, the Committee could not endorse these statements.

The Policy Guide draft will need to be revised to reflect the changes being made in the Risk Assessment. If the Committee is to review the Policy Guide again, it should be sent to the Committee with a supporting document that explicitly states the technical basis for each of its summary statements on the state of scientific knowledge.

5.0 SPECIFIC REVIEW ISSUES

5.1 Lung Cancer in Adults The Committee noted that Chapters 3 and 4 addressed the issue of lung cancer risk due to spousal smoking only for non-smoking women. It is suggested that the revised document be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where substantial improvements could be made in the organization of the document, as well as in its content -- some material was not adequately covered or not addressed at all. The Committee urges the EPA to redraft those chapters as well. Some specific suggestions follow.

5.1.1 Carcinogenicity of ETS The Indoor Air Quality and Total Human Exposure Committee concurs with the finding of the draft report that Environmental Tobacco Smoke (ETS) should be classified as a Class A Carcinogen. The Committee believes, however, that the case could be made more persuasively than does the current draft document. Part of the difficulty may be found in the language and the rationale of the Guidelines for Carcinogen Risk Assessment as they are currently formulated (51 FR 33992, August 22, 1986). The Guidelines address the case of a single chemical compound which may contain contaminants or impurities. The process envisioned in the Guidelines consists of Hazard Identification and "..should include a review....to the extent that it is available" of:

1. Physical-Chemical Properties and Routes and Patterns of Exposure
2. Structure-Activity Relationships
3. Metabolic and Pharmacokinetic Properties
4. Toxicologic Effects
5. Short-Term Tests
6. Long-Term Animal Studies
7. Human Studies

In the Guidelines, the Long-Term Animal Studies section is covered in 25 column-inches, and the Human Studies section takes up about seven column-inches, an indication of the emphasis on long-term animal toxicology studies.

The evidence for the carcinogenicity of tobacco smoke is not based on long-term animal studies, which are negative. In this case, the strongest evidence is that obtained in a large number of epidemiologic studies of active smoking and lung cancer. The causality of the connection between inhalation of tobacco smoke and excess risk of lung cancer cannot be in doubt. It has been

demonstrated that cessation of inhalation of tobacco smoke leads to a reduction of the excess lung cancer risk. The risk has been shown to be proportional to the amount of smoke inhaled. In terms of overall impact it has been shown that a very high proportion of the observed lung cancer incidence is due to inhalation of tobacco smoke. If the Guidelines for Carcinogenic Risk Assessment can be used to cast doubt on a finding that inhalation of tobacco smoke by humans causes an increased risk of lung cancer, the situation suggests a need to revise the Guidelines.

The inhalation of ETS by children, by non-smokers or former smokers represents a risk that is much smaller than that experienced by active smokers, but it is an involuntary exposure. It is not uncommon to derive quantitative risk assessments of exposures to carcinogens from data obtained in more heavily exposed occupational populations, and in that sense smokers represent a more heavily exposed population, providing data for extrapolation to the lower exposures imposed on children and adult non-smokers.

There are both differences and similarities in the characteristics and the composition of mainstream smoke, sidestream smoke, exhaled tobacco smoke and environmental tobacco smoke. It is important to deal both with the differences and similarities as they might affect the quantitative risk which is most accurately known for mainstream smoke. The difference in carcinogenic potential is not such that any one of these other categories could be considered as non-carcinogenic in humans. The very clear carcinogenicity of mainstream tobacco smoke directly implies carcinogenicity of ETS, particularly in view of the similarities in chemical composition and sizes of particulates between mainstream and sidestream smoke.

Meta-analyses of epidemiologic studies in non-smokers and former smokers are sensitive to decisions about exclusions and inclusions, and are primarily oriented towards increasing the overall statistical power and more precisely describing risk. Such analyses cannot effectively take into account any differences in quality of the study, differences in the way exposures were determined or classified, etc. Biases will be reduced only in that they will be averaged.

5.1.2 <u>Spousal Smoking</u> All of the studies cited in the report on ETS and risk of lung cancer have made observations on married women

who have been classified as "never-smoking". Those married to a smoker are assumed to be exposed to greater levels of ETS than those married to a nonsmoker (p.3-12). As noted in the report, this relative risk comparison implicitly compares women exposed to both spousal and other ETS to those exposed to other ETS only.

The ideal measure of ETS exposure for lung cancer studies would include all sources of ETS with data on both dose of ETS and exposure over time for a lifetime, or at a minimum over the past 20 to 30 years. Spousal smoking is believed to be a useful and valid marker for ETS exposure because (1) it often indicates many years of exposure (this contrasts with biological markers such as urinary cotinine, which indicate exposure at only one point in time); (2) the level of ETS exposure in the home when the spouse smokes appears to be greater in magnitude than the exposure from other, non-domestic, sources. Several studies exploring urinary cotinine as a measure of ETS exposure have found higher levels in non-smokers married to smoking spouses than to those married to nonsmoker spouses. The statement that ETS in the home is greater than that of other ETS exposures may be more or less true according to a variety of factors as noted below. The use of spousal smoking data is highly attractive because such data are easy and inexpensive to collect. For most studies spousal smoking is the only available measure of ETS exposure.

There are potential limitations in the use of spousal smoking as an indicator of ETS exposure that need to be considered:

1. Spousal smoking may account for a relatively small proportion of lifetime ETS exposure. Janerich et al. (1990) estimated that spousal exposure accounted for only 30% of lifetime exposure. These authors computed correlation coefficients of 0.37 and 0.51 between spousal smoking and lifetime ETS exposure for men and women, respectively. In this study childhood exposure was a major source of lifetime ETS exposure and correlated more highly with lifetime exposure. Likewise, Cummings et al. (1989) found little relationship between childhood, adult home and work place ETS exposure. On the other hand, Thompson and co-workers (1990) found that non-smokers who lived with a smoker reported more ETS exposure outside of the home than those who did not live with a smoker. In this way spousal smoking could be a more general indication of ETS exposure than

expected on the basis of exposure in the home per se, but sensitivity for total ETS exposure may vary among different study populations.

2. The results of comparing ETS household exposure to ETS household plus other exposures may vary in different countries and different regions within the U.S. Exposure within the residence depends on size and the type of construction of the dwelling, the amount of ventilation, and the proximity of smokers and nonsmokers within the home. Non-domestic background exposure varies with the nature of their workplace exposures, the extent of smoking restrictions in the work place and public places, the climate and the time of the year. With respect to the latter, exposures as assessed by urinary cotinine concentrations in Buffalo, New York were greater in the winter compared to the summer, presumably due to more time spent indoors with less ventilation in cold weather (Cummings et al., 1989). Such differences would be expected to be less marked in warmer regions of the country. For non-smoking people in particular, the extent of exposure outside of the home may depend on whether the woman works and how many other people in the population, who may be friends of non-smoking women, smoke. Thus, in countries such as Japan where fewer women work outside of the home, and fewer women in general smoke, spousal smoking may indicate differential exposure for women who are, and who are not exposed to ETS, than in the U.S. In any case, bias due to concerns (1) and (2) would decrease the difference in true exposure between the "exposed" and "non-exposed" nonsmoking spouses, and would favor finding no difference in relative risk. These issues may explain some of the variability found in relative risk for lung cancer with ETS exposure in different countries around the world.

3. As noted previously, a major source of ETS exposure is that incurred in childhood, which could contribute to increased lung cancer risk in an adult. Although not generally specified in quantitating the risk of having a smoking spouse, it is possible that a person whose parent(s) smoked (and therefore who was exposed to ETS as a child) is more likely to marry a smoker. In this case the risk of ETS might

reflect the risk of combined childhood and spousal exposure rather than just exposure to the spouse.

4. The use of spousal smoking as an indicator of exposure may amplify the risk of misclassification of smokers as non-smokers. There appears to be a concordance between spousal smoking and false reporting of current or former smoking status. The misclassification of smoking status would falsely increase the relative risk of lung cancer in non-smokers related to ETS exposure. The misclassification issue is considered in detail in the report and appropriate corrections have been made for misclassification.

5. Spousal smoking status could be associated with several sources of potential confounding. For example, it is possible (although not documented by specific studies) that the presence of a smoking spouse is associated with an increased likelihood of lower socio-economic class, dietary differences, more alcohol or other drug exposure, more exposure to air pollution, etc. Such factors could possibly increase the risk of lung cancer, and published epidemiologic studies have addressed these factors to varying degrees. The potential sources of confounding based on spousal smoking status should be discussed in the report, with a recommendation that future studies explicitly address these issues.

In summary, considering its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a reasonable method of identifying people with greater, versus lesser, ETS exposure. The problems in not accounting for background exposure would, if anything, bias against finding increased risk of lung cancer. Bias related to misclassification associated with smoking status has been addressed and corrected for in the draft report. There are possible confounders related to spousal smoking status, but such confounding concerns are present in other surrogates of exposure as well study. The importance of these confounders has not been determined to be sufficient to alter the conclusion that ETS increases the risk of lung cancer.

5.1.3 <u>United States and Foreign Studies</u> The Committee felt that data from studies conducted overseas as well as in the United States should be utilized in evaluating whether exposure to ETS

increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted. The Committee commented that the text of Chapter 3 of the report seemed to overemphasize the Japanese cohort study, but felt that this and other non-U.S. investigations were directly relevant to establishing that ETS is a carcinogen for lung tissue.

Given the variety of study settings and the potential for differences in exposure to ETS between (and even within) countries, it is not surprising that relative risks vary from study to study. The higher relative risks found in some studies outside the United States may in part be related to differing characteristics of exposure to spousal smoking, differences in background ETS levels, or still other variables. The Committee believes that the report should recognize such potential differences, although adjustment for them may be precluded by lack of detailed ETS exposure data in the various studies. We do not disagree with the draft report's approach of incorporating data from around the world in estimating the numbers of lung cancer deaths in this country due to ETS, but believe that the estimates should be interpreted cautiously. In this regard, we recommend that the assumptions used, and their accompanying uncertainties in estimating numbers of lung cancer deaths attributable to ETS, be underscored.

5.1.4 <u>Use of Meta-Analysis</u> Meta-analysis is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS. However, the priority given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Evidence on the carcinogenic effect of active smoking, the presence of carcinogens in ETS, and predicted lung cancer risk of low dose exposure to tobacco smoke from appropriate models, are an important part of establishing a causal relationship. The meta-analysis could then be interpreted as showing the available epidemiologic evidence is consistent with a small elevated risk.

Meta-analysis is a general term applied to a wide range of techniques whose objective is to synthesize findings across related studies. Although, there is still considerable debate over many aspects of conducting a meta-analysis, several criteria are usually considered essential. These include: 1) clear statement of the objective of the meta-analysis; 2) precise definition of criteria

used to include (or exclude) studies; 3) critical review of studies included in the analysis; and 4) assessment of the effect of individual studies on the analysis. Many of these points were not adequately addressed in the meta-analysis provided in the EPA document.

The authors of the draft report did not provide a precise statement of the role of the meta-analysis. In regard to general methodology, there are several roles a meta-analysis might play. Bangert-Drowns (1986) distinguishes five different types of meta-analyses depending on the question to be addressed. In the EPA draft report, the consistency of the various studies is addressed, an attempt is made to estimate overall risk, the possibility of heterogeneity of study results is considered, and geographic variation is discussed as a possible source of heterogeneity. Unfortunately, it is not clear which of these issues is the primary target of the analysis. If it was intended to address all four issues, they were inadequately covered. In regard to consistency of findings (which is probably the most important issue), the findings were not presented in the most appropriate way. Estimates with corresponding confidence intervals are the most generally acceptable method of presentation. If the intention was to investigate heterogeneity, then formal tests of heterogeneity should have been provided. If it was intended to address the hypothesized U.S./foreign difference, it would have been useful to test the difference in risk between the two sub-groups of studies.

Specific criteria for including studies was not provided. The importance of this was reinforced at the Committee meeting when a reanalysis was presented on a different set of studies than those in the report. This resulted in a change in the overall risk estimate. Decisions as to study inclusion should be made <u>prior</u> to analysis, based on clearly stated criteria. It is also desirable to evaluate the impact on conclusions of closely related, but excluded, studies.

Finally, in testing the hypothesis of an elevated relative risk across studies, the reliance on the measure of "x-number of studies rejecting out of n" as the basis for the p-values seems somewhat arbitrary and inefficient. It would be preferable to use the sum of the S-statistics given in the report as a test statistic.

5.1.5 Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The variables included in these adjusted analyses were age, education, and social class. Comparison of unadjusted and adjusted Rrs in those studies which present both, suggests that these variables are relatively unimportant.

There is no way to evaluate the importance of occupation, radon exposure, and diet as confounders of the ETS-lung cancer relationship, or to adjust for them, since virtually none of the studies contain information on them. However, they could be mentioned in the text as potential confounders.

The issue of misclassification should not be restricted to misclassification of current and ex-smokers as "never smokers." It should also be mentioned that non-differential misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

The misclassification of smoking status is differential in that current smokers and (particularly) ex-smokers are apt to be reported as "never smokers," whereas the reverse is unlikely.

The adjustment for misclassification of smokers as nonsmokers in the Report makes use of the formula used by the National Research Council for prospective studies, but no rationale or explanation for the formula is given in either Chapter 4 or Appendix B (Note also that several errors have been pointed out in the formulae given in Appendix B). Also, no distinction is made between prospective and case-control studies. In the latter, in order for bias due to misclassification of active smoking status to occur, there has to be differential misclassification between cases and controls.

Finally, not enough attention is given in the draft report to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null.

Other potential biases which deserve mention include recall bias (differential reporting of exposure status by cases compared to controls) and bias due to the use of proxy respondents.

5.1.6 Characterization of Uncertainties Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS; and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer appears to argue for a positive effect. With exposure levels that are usually quite low, it is not surprising that the association is weak in many studies and in the aggregate, although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

The biological plausibility argument depends upon establishing: (a) cigarette smoking's known carcinogenic effects; and (b) ETS's resemblance to mainstream tobacco smoke in terms of particle size distribution and composition of carcinogens, co-carcinogens and tumor promotors.

(a) Cigarette smoking's known effects. The document would benefit from a more complete presentation of the evidence concerning mainstream tobacco smoke's role in causing lung cancer. More detailed consideration of the dose-effect relationship for inhaled tobacco smoke would better set the stage for presenting evidence concerning the biological plausibility that exposure to ETS has similar, albeit lesser, health effects.

(b) ETS's resemblance to mainstream tobacco smoke. The ageing of tobacco smoke influences its uptake and deposition in the lung and its potential carcinogenicity. Nonetheless, there are strong similarities in the chemical and in vitro biological activity of ETS and mainstream tobacco smoke. These similarities should be discussed in

the context of other complex mixtures, e.g., coke oven emissions, and diesel exhaust (The work of Lewtas at EPA should be revisited for this purpose). The uncertainties surrounding the evidence regarding changes in sidestream smoke composition should be assessed and the implications of such findings for the biological plausibility argument should be spelled out more thoroughly.

Epidemiologic evidence on the relationship between exposure to ETS and lung cancer should be described more completely, with the deficiencies of individual studies used to weight their contributions to any conclusions that are drawn. The assumptions and uncertainties associated with each step of the risk assessment process ought to be explicitly stated.

Not all the factors that probably contribute to the uncertainties surrounding the estimates of deaths attributable to ETS exposure are now considered. For example, it is important to justify the use of the particular biological marker chosen to estimate relative exposures (and, therefore, premature deaths) in passive versus active smokers, since that choice can cause the attributable deaths figure to vary over a twenty-fold range. Consequently, any estimate of the number of deaths to be expected each year from exposure to ETS should be justified more adequately than is now the case. A graphical presentation would clarify the uncertainties associated with each step as well as those inherent in the final estimate of attributable deaths.

As noted in Section 3.2, the cigarette-equivalent approach has a great advantage in that it is based on relatively sturdy RR determinations in active smokers, which can be used to project the risk (in the form of a percentage of the risk in active smokers) to nonsmokers exposed to ETS. However, the assessment of the cigarette-equivalent in non-smokers due to exposure to ETS has a considerable level of uncertainty embedded in it, i.e., about an order of magnitude. Neither cotinine nor smoke particulate levels are adequate direct indicators of carcinogenic components.

The other type of exposure assessment is based on inferences from the epidemiologic studies. Since spousal smoking is a very important exposure proxy used in many studies, there is concern about how usable this categorical classification is for quantitative exposure assessments. Physical proximity, daily length of

exposure, and exposure outside the home to ETS may be quite different in different cultures and over decades of time. Misreporting of smoking status in the cases in some studies also introduces a bias. Various attempts have been made to apply corrections for these biases.

Both the relative potency approach and the cigarette equivalent approach share an implicit assumption that particle phase compounds, and polynuclear aromatic hydrocarbons in particular, are the carcinogens of interest. However, other carcinogens have been identified in ETS, and many of these are in the vapor phase (refer back to Section 3.7 for a full description). To the degree that vapor phase carcinogens have been ignored, or incompletely collected or extracted for experiments, the potency of ETS has been underestimated.

Another consideration is that the relative potency in animals is not necessarily the same as the relative potency in humans. The complexities of tobacco emissions complicate the cigarette equivalent approach. The referent mainstream emissions should be those of unfiltered cigarettes, upon which most of the active smoking epidemiologic data is based. The variable ratios in sidestream to mainstream emissions of toxins lead to differences in the calculated cigarette equivalents to which a passive smoker is exposed. These different emission ratios are one source of variability in the ratio of biomarkers in smokers and nonsmokers. For example, cotinine in nonsmokers is typically less than 1% of the level found in smokers, while the median level of 4-aminobiphenyl hemoglobin adducts in nonsmokers was 14% of the median in smokers. Furthermore, DNA adducts are subject to repair mechanisms, and the rate of repair may differ in smokers and nonsmokers.

5.1.7 <u>Quantitative Risk Assessment</u> The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis was a suitable approach to combining the data. This approach is the most direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended:

1. Criteria for Including Individual Studies in the Meta-analysis

Criteria to include or exclude individual studies from the meta-analysis should be determined and explicitly stated (See section 5.1.4, preceding). The effects of individual excluded studies on the quantitative risk assessment should be evaluated and discussed. The power of the individual studies should also be considered and discussed.

2. Adjustment for Smoker Misclassification

The rationale for the formula used to adjust for smoker misclassification should be given. Appropriate distinctions should be made in applying the misclassification formula to the case-control and the cohort studies. Because of the marriage aggregation factor -- the greater tendency for smokers to marry smokers -- the misclassification of some smokers as nonsmokers can artificially inflate the relative risk of lung cancer associated with passive smoking in cohort studies. In case control studies, misclassification by itself is not enough to inflate the relative risk. Differential misclassification, with cases mis-reporting more frequently than controls, is needed. The assumptions used in adjusting for smoker misclassification and their effect on the adjustment should be more fully discussed. If the approach taken is conservative, then it is noteworthy that the misclassification adjustment only lowers the relative risk estimate from a little over 1.4 to 1.3.

3. Misclassification of Exposure

Some unexposed women, classified as un-exposed (non-smokers married to non-smokers) may in fact be exposed to relatively high levels of ETS in the workplace or in other settings outside of the home. Some recent of non-smokers' exposure to nicotine indicate variations in exposures ranging over two orders of magnitude. Correction for "background" exposure does not adequately correct for this misclassification. Furthermore, the use of spousal smoking habits to classify ETS

exposure status is more likely to misclassify American women's exposure than Japanese women's exposure because of differences in American and Japanese lifestyles. Non-smoking American women married to non-smokers are more likely to be exposed to ETS outside of the home than are Japanese women because more American women work outside the home and have friends who smoke. Some evaluation of the effects of these biases would be appropriate in the risk estimations.

4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking

The uncertainty in the relative risk estimate of lung cancer due to passive smoking is based only on statistical considerations. There are other uncertainties that influence this estimate. A more critical analysis of the potential for systematic bias should be done. Acknowledging such uncertainties would provide greater balance to the report, while not substantially altering its overall message.

5. Dose-Response Estimation of Risk

There are many more assumptions and uncertainties in any risk estimation made on the basis of dose-response or dosimetry than for epidemiologic data. Nonetheless, such an estimate may be of value if the assumptions are fully stated and the uncertainties in the estimate are quantitatively estimated. With uncertainty estimates explicitly included, this approach may well be consistent with that based on epidemiology. Exposure estimates for ETS should include the exposures from birth to age 15, not only from age 15 on up as is done for mainstream smoking. This can have a substantial impact on the estimated risk. Complex dosimetry models should be considered the subject of research at this point in time, since they require many more assumptions.

6. Dose-Response Model for ETS-Radon Interaction Effects

Development of a specific dose-response model for ETS-radon interactions is not recommended. The interactions of ETS with radon are numerous and involve both physical and biological interactions which are not fully understood at present. Fur-

thermore, there are no relevant epidemiological data concerning such interactions.

5.1.7 **Home vs. Workplace Exposure** The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and its importance in relation to total ETS exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area. The report should also review and comment on the data that exists on exposure to ETS in public places.

The Committee also recommends that EPA staff discuss possible approaches for estimating the exposure of children to ETS in homes with one or more smoking parents. This is recommended because of the potentially large public health impact of respiratory disorders in children that may be caused by exposure to ETS. Careful consideration should be given to the differences in the exposure parameters required for lung cancer as opposed to respiratory disorder assessments. For example, cancer assessment may require integrating exposures over longer time intervals than does the assessment of respiratory disorders. Besides developing approaches for estimating average child population exposures, it is also important to establish the shape of the exposure distribution, particularly the tail of the distribution, in order to determine whether a numerically significant subset of children is at high risk.

5.2 Respiratory Disorders in Children

Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantively improved and that the conclusions drawn could be made much stronger if the chapter is revised in the manner suggested in Section 3.3.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than stated in Chapter 5 of the draft ETS Risk Assessment document, and recommends that the new draft contain a chapter devoted to quantitative risk assessment, in terms of the number of children at risk for various outcomes. It would be analogous to Chapter 4, which deals only with the evidence for lung cancer risk discussed in Chapter 3. The risks are different, but it is possible that the

impact of ETS on respiratory health in children may have much greater public health significance than the impacts of ETS on lung cancer in nonsmokers.

There will need to be new material in the earlier chapters on lung dosimetry and the physical and chemical factors affecting it. The difference in deposition and retention of ETS components between children and adults need to be recognized and considered in a risk assessment.

5.2.1 Weight of Evidence The scope of Chapter 5 is limited to selected studies published subsequent to the 1986 Surgeon General's Report and the National Research Council Report. Neither of these reports judged the associations of ETS exposure and children with adverse respiratory effects to be causal; alternative explanations for the associations including confounding and information bias could not be excluded. The additional literature available since 1986 provides a basis for increased concern. Thus, the Committee urges a thorough review of the entire body of evidence. A considered judgment cannot be made concerning causality without assessing the totality of the evidence including studies reviewed in the two 1986 reports and those published subsequently.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed (causality, confounding, information bias) and the individual studies reviewed for the approaches used to address confounding and information bias. The weight of the evidence could then be judged to determine the causality of associations.

With regard to including the reviews of the 26 new reports as Appendix E, the scope of the review should be expanded to include all studies not in the 1986 Surgeon General's Report. A more comprehensive search is needed since the 26 publications identified by the chapter's authors do not represent all significant publications on the effects of ETS on children published since 1986.

5.2.2 Confounders A number of confounders were mentioned by the report, but addressed improperly. These include in utero exposure,

parental reporting bias, and active smoking. The Committee considers the following factors to be critical:

Unreported Smoking
Other Indoor Pollutants
Biological Precursors & Medical Characteristics
Exposure to Biological Agents
Other Exposures (outdoor)
Parental Symptoms
Socio-Economic Factors
Other Sources of Reporting Bias (includes Annoyance Responses)

One must stress the biological precursors important to the effects of ETS in childhood. These include genetic predisposition (physiological, immunological and biochemical), in utero exposure, and breast feeding. These also include environmentally-induced atopy and residua of infections. Pre-existing medical conditions, such as cystic fibrosis, congenital defects will also affect responses to ETS.

The socio-economic and behavioral factors are important as they relate to nutrition (re: resistance), familial crowding, and other contacts (especially day care), medical attitudes and medical care, etc. Socio-economic status (SES) and day care have been shown to modify the effects of ETS.

Reporting bias is a critical issue for ascertaining exposure, as has been documented by many previously. There are two major components to this, the positive bias and the negative bias. The first is thought to occur associated with parental conditions (e.g., Colley, 1974; Cederlof and Colley, 1974). The second is thought to occur because the respondent becomes annoyed by ETS (e.g., Weber 1984; Hugod 19 84; NCHS 1976; NIOSH 1971), and/or have anger/aggression reactions (e.g., Jones and Bogat 1978).

Effects of active/self-smoking interacting with passive smoking should be discussed (Bland et al. 19 78; Lebowitz et al. 1987 and 1988)

Other exposures which have similar effects (e.g., wood smoke, other particulate matter, NO_2, formaldehyde) may be confounding the effects of ETS (Hammer et al. 1976; Anderson 1979; Speizer et al. 1980 (with update); Comstock et al. 1981; Melia et al. 1982; and Koo et al. 1988), or may interact with ETS in producing effects (Lebowitz et al. 1990, and in press). Of course, individuals

including children may have multiple micro-environments in which they are exposed, so insufficient information would tend to yield incorrect exposure-response curves.

Thus, there are many possible co-variates and confounders which should still be considered (Lebowitz 1990).

5.2.3 Use of Meta-Analysis The staff should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of suitable studies for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined in Section 5.1.4.

6.0 SUMMARY AND CONCLUSIONS

In conducting its review of the ETS Risk Assessment document and Policy Guide, the Committee found them to be good faith efforts to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, most of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the documents to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, where it has been necessary to prepare and review two or more draft documents prior to their endorsement by the Clean Air Scientific Advisory Committee (CASAC). This Committee has suggested both organizational and specific technical changes and additional analyses that, if followed, can result in improved ETS Risk Assessment and Policy Guide documents, and stands ready to provide further review comments on the revised drafts.

The SAB was asked to address the following issues in reviewing the documents:

A. Lung Cancer in Adults . The Committee noted that Chapters 3 and 4 addressed only the issue of lung cancer risk for non-smoking women due to spousal smoking. The revised document should be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where substantial improvements could be made organizationally, and in terms of content of material that was not adequately covered or not covered at all, and urge the EPA staff to redraft those chapters as well. Comments on specific issues within the broader context of lung cancer follow below.

1. Carcinogenicity of ETS The Committee concurs with the judgement of EPA that Environmental Tobacco Smoke should be classified as a Class A Carcinogen. The Committee had some difficulty with the use of the Guidelines for Carcinogen Risk Assessment as they are currently formulated (51 FR 33992 August 22, 1986).

The strongest evidence for the carcinogenicity of tobacco smoke is that obtained in a large number of epidemiologic studies

of smoking and lung cancer. The causality of the connection between direct inhalation of tobacco smoke and excess risk of lung cancer cannot be in doubt. It has been demonstrated that cessation of inhalation of tobacco smoke leads to a reduction of the excess lung cancer risk. The risk has been shown to be proportional to the amount of smoke inhaled. In terms of overall impact it has been shown that a very high proportion of the current lung cancer incidence is due to inhalation of tobacco smoke. The ageing of sidestream tobacco smoke influences its uptake and deposition in the lung and its potential carcinogenicity, but there are strong similarities in the chemical and in vitro biological activity of ETS and mainstream tobacco smoke, and ETS resembles mainstream tobacco smoke in terms of particle size distribution and composition of carcinogens, co-carcinogens and tumor promotors.

The inhalation of ETS by children, by non-smokers or former smokers represents a risk that is much smaller than that experienced by smokers, but it is an involuntary exposure. It is not uncommon to derive quantitative risk assessments of exposures to carcinogens from data obtained in more heavily exposed occupational populations, and in that sense smokers represent a more heavily exposed population which can be used for extrapolation to the lower exposures imposed on children and non-smokers.

2. Spousal Smoking All of the studies cited in the report on ETS and risk of lung cancer have made observations on married women who have been classified as "never-smoking." Those married to a smoker are assumed to be exposed to greater levels of ETS than those married to a nonsmoker. As noted in the report, this relative risk comparison is implicitly a comparison of women exposed to both spousal and other ETS to those exposed to other ETS only.

Spousal smoking is believed to be a useful maker for total ETS exposure because (1) it often indicates many years of exposure: this contrasts with biological markers such as urinary cotinine, which indicate exposure at only one point in time; (2) the level of ETS exposure in the home when the spouse smokes appears to be of substantially greater magnitude than the background exposure.

There are potential limitations in the use of spousal smoking as an indicator of ETS exposure that need to be considered:

1. Spousal smoking may account for a relatively small proportion of lifetime ETS exposure.

2. The difference in ETS exposure comparing household exposure versus household plus background exposure may differ in different countries and different regions within the U.S.

3. A major source of ETS exposure is that incurred in childhood, which could contribute to increased lung cancer risk in an adult.

4. The use of spousal smoking as an indicator of exposure may amplify the risk of misclassification of smokers as non-smokers.

5. Spousal smoking status could be associated with several sources of confounding, e.g., lower socio-economic class, diet, alcohol, drugs, more exposure to air pollution, etc., factors that could possibly increase lung cancer risk.

Despite various limitations as an indicator of ETS exposure, spousal smoking status is a reasonable method of identifying people with greater, versus lesser, ETS exposure.

3. **United States and Foreign Studies** The Committee felt that data from studies conducted overseas as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. **Use of Meta-Analysis** Meta-analysis is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS. However, the priority given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Evidence on the carcinogenic effect of active smoking, the presence of carcinogens in ETS, and predicted lung cancer risk of low dose exposure to tobacco smoke from appropriate models are an important part of establishing a causal relationship. The meta-analysis could then be interpreted as showing the available epidemiologic evidence is consistent with a small elevated risk.

5. Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the Report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The main confounders included in these adjusted analyses were: age, education, and social class. Comparison of unadjusted and adjusted RRs in those studies which present both, suggests that these variables are not important confounders.

As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust for them, since virtually none of the studies contains information on them. However, they could be mentioned in the text as potential confounders.

The issue of misclassification should not be restricted to misclassification of current and ex-smokers as "never smokers." It should also be mentioned that misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

Not enough attention was given to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null. Other potential biases which deserve mention include recall bias (differential reporting of exposure status by cases compared to controls) and bias due to the use of proxy respondents.

6. Characterization of Uncertainties The draft risk assessment document's findings on the ETS/adult lung cancer relationship is based on two main arguments: (1) biological plausibility; and (2) epidemiologic evidence. With exposure levels that are usually quite low, it is not surprising that the association is likely to be weak although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great impor-

tance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. **Quantitative Risk Assessment** The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis was a suitable approach to combining the data. It is direct and makes few assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended with respect to:

1. Criteria for Including Individual Studies in the Meta-analysis
2. Adjustment for Smoker Misclassification
3. Misclassification of Exposure
4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking
5. Dose-Response Estimation of Risk

8. **Home vs. Workplace Exposure** The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace. However, the report should review and comment on the data that do exist.

B. **Respiratory Disorders in Children** Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantially improved and that the conclusions drawn in it could be made much stronger if the chapter was revised in the manner suggested in this report.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than that stated in Chapter 5 of the draft ETS Risk Assessment document, and

recommends that the new draft contain a chapter devoted to quantitative risk assessment. It would be analogous to Chapter 4, which deals only with the evidence for lung cancer risk discussed in Chapter 3. The risks are different, but it is possible that the impact of ETS on respiratory health in children may have much greater public health significance than the impact of ETS on lung cancer in nonsmokers.

The earlier chapters on lung dosimetry and the physical and chemical factors affecting it should incorporate new material. The difference in deposition and retention of ETS components between children and adults need to be established and considered in a risk assessment.

Comments om specific issues follow:

1. **Weight of Evidence** The scope of Chapter 5 is limited to selected studies published subsequent to the 1986 Surgeon General's Report and the National Research Council Report. The additional literature available since 1986 provides a basis for increased concern. Thus, the Committee urges a thorough review of the entire body of evidence. Judgment cannot be made concerning causality without assessing the totality of the evidence including studies reviewed in the two 1986 reports and those published subsequently.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed (causality, confounding, information bias) and the individual studies reviewed for the approaches used to address confounding and information bias. The weight of the evidence could then be judged to determine the causality of associations.

2. **Confounders** A number of confounders were mentioned by the report, but addressed improperly, such as *in utero* exposure, parental reporting bias, and active smoking.

The biological precursors important to the effects of ETS in childhood include genetic predisposition (physiological, immunological and biochemical), *in utero* exposure, and breast feeding. These also include environmentally-induced atopy and residua of

infections. Pre-existing medical conditions, such as cystic fibrosis, congenital defects will also affect responses to ETS.

The socio-economic and behavioral factors are important as they relate to nutrition (re: resistance), familial crowding and other contacts (especially day care), medical attitudes and medical care, etc. SES and day care have been shown to modify effects of ETS.

3. Use of Meta-Analysis The staff should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there was a body of suitable studies for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined for meta-analysis for lung cancer.

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