# HEALTH EFFECTS OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

## APPENDIX A
## SUMMARY OF PUBLIC COMMENTS AND RESPONSES

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

# Appendix A: Summary of Public Comments and Responses

## Table of Contents

# DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

## Perinatal Manifestations

**P.N. Lee, for the Tobacco Institute:**

1. Comment**:** Relevant evidence

Evidence of effects from maternal smoking are not relevant as the exposure to ETS is minimal and analyses of ETS effects must be restricted to those on nonsmokers.

Response: Every effort has been made to separate observations of effects of active smoking from those of ETS exposure. Information regarding effects of active smoking were included for comparative purposes; qualitative and quantitative differences between the two sources are acknowledged.

2. Comment: Perinatal mortality

Commenter briefly describes eight studies which investigated the association of prenatal smoking or ETS exposure with perinatal mortality, but notes that "they do not provide convincing evidence that ETS exposure has an adverse effect."

Response: It is agreed that such concerns are justified given the limited number of available studies and the inconsistency of their findings (see Executive Summary p. ES-5).

3. Comment: Birth defects

The commenter reviews the available data concerning ETS exposure and birth defects and concludes that "the overall evidence does not convincingly demonstrate any association between paternal smoking and any specific kind of birth defect."

Response: A similar conclusion has been reached in Chapter 3 with the statement that "[d]ue to the limitations in assessing exposure in the existing studies, it is not possible to determine whether there is an association of ETS exposure with birth defects."

4. Comment: Low birth weight

"The evidence relating birth weight to either paternal smoking or maternal ETS exposure has been less studied [than that of active maternal smoking], and has not provided any clear evidence of an association."

Response: There is a large body of literature available from which conclusions can be drawn regarding the effects of paternal smoking or maternal ETS exposure. In making the evaluation of the weight of evidence for this effect, more than twenty-five epidemiological studies were reviewed. Of the studies which examined mean birthweight, all but one showed a decrement with ETS exposure. Although the effect, when observed, was frequently small, the data in sum support a causal association of ETS exposure with increased low birth weight (LBW) or intrauterine growth retardation (IUGR).

5. Comment: The commenter notes that one would expect "a few studies to report a statistically significant finding even if no true association exists at all."

Response: Several of the studies described in the ETS document have shown statistically significant associations of ETS exposure with mean low birth weight. Of the available studies, only a few of the studies showed a statistically significant association for the odds ratio (OR). Individual studies have different strengths and weaknesses and when the all the studies are taken together, they support a slight increase in LBW or IUGR in association with ETS exposure. The most convincing evidence comes from biomarker studies, followed by studies that attempted to ascertain ETS exposure from multiple sources and adequately controlled for confounding.

6. Comment: The commenter notes that "it seems unlikely that any study has adequately controlled for confounding, bearing in mind the difficulty of knowing all the relevant variables and of measuring them accurately."

Response: The number of potential confounders in any given epidemiological study is large. However, a number of relevant confounders have been identified and are adequately adjusted for in many of the important studies. Among those variables which have been considered in the various studies are: maternal age, parity, ethnicity, maternal weight, history of LBW offspring, income, and caffeine intake. Furthermore, the evidence relating ETS exposure to low birth weight is also strengthened by the consistency of the findings among studies of international origin, the observation of a dose-response in several studies, and findings in animal studies.

7. Comment: The commenter states concern regarding smoking habit misclassification.

Response: Smoking habit misclassification is a concern that has been addressed in different parts of the ETS document with respect to various epidemiological studies. Efforts have been made to evaluate studies for consistency in terms of the magnitude of this confounder and we believe that, in spite of this source of error, the studies on the whole provide evidence for causality in the association between ETS exposure and low birth weight. Studies have indicated that questionnaire responses generally provide reliable qualitative information on smoking.

8. Comment: The commenter states concern regarding the magnitude of the observed effect given the "much smaller exposure of the fetus to smoke constituents when the mother is ETS exposed than when she smokes", stating that the effect is implausibly large.

Response: The relationship between effects seen with active smoking and ETS-related effects is not necessarily linear and effects from ETS do not represent simply an adverse effect "scaled-down" using a particular biomarker to calibrate from active smoking to ETS exposure.

**Mary E. Ward of R.J. Reynolds**

Comment: The commenter presents a copy of comments which were provided to OSHA concerning the federal OSHA docket on its Notice of Proposed Rulemaking on indoor air quality. Among the concerns raised are the inequality of ETS and mainstream smoke, the timing of exposure, misclassification of exposure, adjustment for confounding, and the usefulness of

animal studies. The commenter concludes that "[t]he available evidence is not sufficient to conclude that exposure of nonsmokers to ETS results in either measurable deficits in reproductive capacity and/or measurable deficiencies in affected offspring."

Response: Although the comments provided do not directly address the ETS document, they describe issues which were important in evaluating the evidence for developmental effects from ETS exposure. In the ETS document, data from studies with active smoking were included for comparative purposes only, and ETS and mainstream smoke were not considered equal. The potential effects of maternal smoking during pregnancy was addressed where appropriate. Classification of exposure requires that the occurrence and duration of exposure to all sources of ETS are ascertained as completely as possible. The potential involvement of misclassification as a source of error was evaluated on a study-by-study basis in determining the overall weight of evidence for a given effect. A number of relevant confounders have been identified and are adequately adjusted for in many of the important studies

**Raphael and Philip Witorsch of the Center for Environmental Health and Human Toxicology, Washington, DC, for the Tobacco Institute**

1. Comment: Birthweight:
The commenters have concerns about misclassification error and confounding in the 32 available studies. The commenters also summarize and describe limitations of many of these studies.

Response: Smoking habit misclassification is a concern that has been addressed in different parts of the ETS document with respect to various epidemiological studies. Effort has been made to evaluate studies for consistency in terms of the magnitude of this confounder and we believe that, in spite of this source of error, the studies on the whole provide evidence for causality in the association between ETS exposure and low birth weight. Studies have indicated that questionnaire responses generally provide reliable qualitative information on smoking. We also acknowledge that the number of potential confounders in any given epidemiological study is large. However, a number of relevant confounders have been identified and are adequately adjusted for in many of the important studies. The evidence relating ETS exposure to low birth weight is also strengthened by the consistency of the findings among studies of international origin, the observation of a dose-response in several studies, and findings in animal studies.

2. Comment: Fetal mortality The commenters summarize and state concerns regarding the seven studies available on ETS exposure as a risk factor for fetal mortality.

Response: Concerns are justified given the limited number of available studies and the inconsistency of their finding, however, some of the epidemiological evidence does support a role for ETS exposure in the etiology of spontaneous abortion. The evidence associating ETS and neonatal mortality is too limited to draw conclusions.

3. Comment: Birth defects The commenter summarizes and states concerns regarding the six studies available regarding ETS exposure as a risk factor for birth defects.

Response: Similar concerns are expressed in the document regarding the available studies examining the relationship between ETS exposure and birth defects. As a result of these limitations, particularly in assessing exposure, it was concluded that it is not possible to determine whether or not a causal association exists.

**Gio Batta Gori of the Health Policy Center, Bethesda, MD, for the Tobacco Institute**

1. Comment: Birthweight The commenter states concerns regarding smoker misclassification error and summarizes the studies examining the relationship of ETS exposure to birthweight. In summary, "the numerous studies are undeniably much too heterogeneous, and an attempt to lump them together is inappropriate." The commenter also suggests a regrouping of the studies which would be more plausible.

Response: Smoking habit misclassification is a concern that has been addressed in different parts of the ETS document with respect to various epidemiological studies. Effort has been made to evaluate studies for consistency in terms of the magnitude of this confounder. In spite of this source of error, the studies on the whole support the evidence for causality in the association between ETS exposure and low birth weight. Studies have indicated that questionnaire responses generally provide reliable qualitative information on smoking.

2. Comment: Other Intrauterine growth retardation (IUGR) is the only condition associated with active smoking with any consistent significance.

Response: Among the perinatal manifestations of developmental toxicity associated with ETS exposure, as well, increased IUGR shows the strongest evidence. Epidemiological studies, supported by evidence in animals studies, provide sufficient evidence that ETS exposure adversely effects fetal growth.

3. Comment: Studies of other reproductive and developmental endpoints for active and passive smoke exposures report weak and contradictory signals, compatible with slight increases or decreases of risk.

Response: Such inconsistencies in the data for specific types of effects have been noted in the document, where appropriate, and these inconsistencies have been evaluated in making conclusions regarding the overall weight of evidence for these effects.

**Richard A. Carchman of Philip Morris**

1. Comment: Commenter states that "the authors of the Review Draft have intermingled data on active smoking with data on ETS exposures throughout the report".

Response: Every effort has been made in the ETS document to separate observations of effects from active smoking from those of ETS exposure. Active smoking data have been included in the document only for comparative purposes

2. Comment: The description of the MacMahon *et al.* study "should make clear when it is referring to data for smokers and nonsmokers combined", likewise for the Magnus *et al*., Borlee *et al.* and Rubin *et al*. studies concerning birth weight effects.

Response: The description of the MacMahon *et al.* (1966) study includes effects observed among the offspring with any paternal smoking and presents a reanalysis limited to nonsmoking mothers. In the other studies, findings specific to those offspring of nonsmoking mothers have been identified.

3. Comment: "..[T]he report appears to be relying on active smoking data in an attempt to strengthen its conclusions on ETS."

Response: The effects of active maternal smoking during pregnancy have been mentioned for comparative purposes in the ETS document. Several of the available studies concerning pregnancy outcome have not separated smokers from nonsmokers in the studied population, but have instead made an effort to control for maternal active smoking. Because of the correlation between spousal smoking habits, however, these studies were not weighted as heavily as those presenting data from ETS exposure of maternal nonsmokers in reaching conclusions.

4. Comment: "The Review Draft includes neither a description nor a definition of ETS nor a discussion of the differences between ETS exposure and active smoking."

Response: A section has been added which appears in Chapter 1 (Introduction) entitled "Definition of ETS." Chapter 2 (Exposure Measurement and Prevalence) discusses some information on the difference between ETS and active smoking.

5. Comment: "...the authors fail adequately to address the numerous published criticisms of the use of questionnaires in assessing ETS exposures."

Response: Studies have indicated that questionnaire responses generally provide reliable qualitative information on smoking. As noted in the chapter, the most convincing evidence of effects of ETS exposure comes from biomarker studies, followed by studies that attempted to ascertain ETS exposure from multiple sources, and adequately controlled for confounding.

6. Comment**:** Many of the factors associated with the endpoints in the Review Draft may be correlated, leading to difficulties in isolating the effect of a single factor.

Response: While it is true that the presence of correlated variables associated with a particular effect makes the observation of a significant effect more difficult, consistency in the findings across numerous studies as well as findings in animal studies has assisted in establishing a greater degree of confidence in evaluating effects associated with ETS exposure.

7. Comment: In the Martin and Bracken (1986) study, the original study population dropped by approximately 2000, introducing potential selection bias.

Response: Among the population determined to be eligible for the study (n=4926), 473 declined to be interviewed, 263 could not be contacted, four gave "unreliable interviews", 76 had indeterminate pregnancy outcomes, 59 did not deliver at the study hospital, and 43 were not singleton deliveries. Given the prospective nature of this study, it is unlikely that these factors would have an important or substantial impact on the findings.

**Jennifer Jinot of the U.S. EPA**
Numerous minor editorial changes were made to the document in response to comments which were provided on a marked-up copy.

1. Comment: "CalEPA's draft chapter is erroneous in downplaying the relevance of the animal studies that use MS [mainstream smoke] rather than SS [sidestream smoke]", given that the commenter considers MS "qualitatively equivalent to ETS for the purposes of hazard identification."

Response: The ETS document has avoided using data from studies of mainstream smoke effects because of qualitative and quantitative differences between ETS and MS. While some animal studies involving exposure to mainstream smoke may provide significant findings of adverse effects, many do not report enough methodological detail concerning exposure to establish their relevance to ETS exposure. Animal models for ETS exposure and data from them are only just becoming available.

2. Comment: "...more weight should be given to the human data from active smoking - not for evidence of effects from maternal smoking on pregnancy, but for analogy with ETS exposure." These types of data provide evidence of fetal uptake of tobacco smoke constituents.

Response: The document has included some human data from active smoking for comparative purposes. However, to avoid the implication that the observed effects from ETS exposure are simply quantitatively scaled-down effects similar to those observed from active smoking, analyses of these data were limited.

3. Comment: The Executive Summary contains no statement regarding the data on the relationship of active maternal smoking and spontaneous abortion, perinatal mortality, and congenital malformation.

Response: Statements regarding data from studies on active maternal smoking have been limited in the Executive Summary because the primary topic of concern is ETS. When relevant, effects of active smoking are mentioned for comparative purposes.

4. Comment: Fetal Growth Effects
The reference Martinez *et al*. (1994) (The effect of paternal smoking on the birthweight of newborns whose mothers did not smoke *Am J Public Health* **84**:1489-1491) should be included.

Response: This study has now been incorporated into the document.

5. Comment: There is no statement as to whether MacMahon *et al*. (1966) controlled for confounders.

Response: The presentation of a 'crude' decrement in birthweight associated with paternal smoking indicates there was no controlling for confounders.

6. Comment: There is no statement as to whether the bivariate regression of Magnus *et al*. (1984) included births to smoking mothers.

Response: Table 3-1, which is a summary table of the studies of birthweight and ETS exposure defined by paternal smoking status, presents the result of this regression analysis in Magnus *et al.* (1984) as a crude difference, implying that this result did include smoking mothers. A analysis described subsequently in the text summary presents the results after adjustment for maternal smoking as well as several other confounders.

7. Comment: There is no indication of the concentration of sidestream and mainstream smoke in several of the animal studies.

Response: Details in this area were minimized in the ETS review document because animal data have not provided the primary weight of evidence. Furthermore, on the basis of the information given in the studies, it was not possible to make comparable estimates of exposure.

**Steven Bayard of the U.S. EPA**

1. Comment: "...the Chapter should contain more information on ETS exposure to newborns, both, in terms of prevalence and biomarkers, than is presented." (especially the Executive Summary).

Response: Information has been added. The location of the information in this area is primarily in Chapter 2 on Exposure Measurement and Prevalence.

2. Comment: The commenter believes the Executive Summary should include the types of effects which can and cannot be adequately studied in epidemiologic studies of ETS exposure.

Response: The ETS document addresses endpoints potentially related to ETS exposure, with some evidence, the bulk of which is epidemiological, for review. Epidemiological investigations suffer numerous limitations, particularly the ability to detect small incremental effects. Throughout the document, information on the limitations of any given study and the database as a whole is presented.

3. Comment: "...the Chapter provides less weight and emphasis to the active smoking or MS [mainstream smoke] studies, than is appropriate."

Response: The document has included some human data from active smoking for comparative purposes. However, to avoid the implication that the observed effects from ETS exposure are

simply quantitatively scaled-down effects similar to those observed from active smoking, analyses of these data were limited.

4. Comment: "...[R]emove the word 'possible' from the SUGGESTIVE category; it is redundant."

Response: The Introduction has been modified accordingly (Section 1.4).

5. Comment: The commenter has concern regarding the statement that animal studies are limited by the exposure assessment difficulties and puts forward that "at least animal studies have some known exposure" and has suggested reconsidering stating the superiority of "nose only" exposure chambers, given the additional stress it may place on the animals. Also, exposure from grooming should not void the findings of the study.

Response: While animal studies do offer the advantage of having known exposure, past studies have been limited by concerns of differentiation between mainstream and sidestream smoke. It is expected that more recently developed animal models will provide data to differentiate between these sources. Ingestion of smoke constituents from fur serves as a complication which can be avoided through the use of nose-only exposure chambers, although it does not completely invalidate the findings of a study. Theoretically, any additional stress on the animals from the use of these chambers could be controlled for in the study.

## Postnatal Manifestations

**P.N. Lee, for the Tobacco Institute**
Comment: The commenter provides an unpublished review which concludes that although the evidence associating parental smoking to the incidence of SIDS is clear, a causal relationship has not been proven. Of particular concern is the effect of adjustment for confounding in the studies.

Response: The section concerned with the effects of postnatal ETS exposure has been updated to include ten studies, six of which examined the relationship of paternal smoking and SIDS, and four of which examined the relationship of household smoke exposure and SIDS. On the strength of the available studies, including two new studies added to the document (Klonoff-Cohen *et al.*, 1995, and Blair *et al.,* 1996) and two earlier well-conducted studies (Mitchell *et al.*, 1993, and Schoendorf and Kiely, 1992) with evidence of a dose-response relationship, there is sufficient evidence that postnatal ETS exposure is an independent risk factor for SIDS.

**Gio Batta Gori, the Health Policy Center, for the Tobacco Institute**
Comment: The commenter provides summaries of many of the available studies regarding the relationship between ETS exposure and SIDS, identifying their shortcomings.

Response: The ETS document discusses the shortcomings and advantages of the available studies as well.

**Maxwell W. Layard of Layard Associates, for the Tobacco Institute**
1. Comment: There is no evaluation/summary of Klonoff-Cohen *et al.* (1995) study which resulted in a change from "suggestive" to "sufficient" of the evidence linking postnatal ETS exposure to SIDS.

Response: The document has been revised to include a summary of the Klonoff-Cohen *et al.* study and the Blair *et al.* (1996) study, along with the earlier studies (now a total of ten) examining the relationship of postnatal ETS exposure and SIDS.

2. Comment: The three sources of ETS (maternal, paternal, and other household) in the Klonoff-Cohen *et al.* study cannot be considered independent estimates "in view of the strong correlation between these smoking sources". An analysis which simultaneously and separately considered these sources was not presented.

Response: The analysis indicates significantly elevated risk associated with each of these sources as well as all three combined. The document has been revised to include summary information from the odds ratios of risks from any maternal smoking, any paternal smoking, any household smoking, as well as same-room smoking from each of these sources relative to infants with no smoke exposure.

3. Comment: The Klonoff-Cohen *et al.* (1995) study is limited by the same factors as the other studies describing this effect, specifically mothers who smoke both during and after pregnancy. Also, it does not restrict analysis to non-smoking mothers. The adequacy of the adjustment for

confounding is questionable. The self-reported maternal smoking data are questionable because of the large discrepancy with another published study (11 and 20% vs. 67% in Gillies *et al.* (1988)).

Response: The study population was of sufficient size to examine the relationship of postnatal maternal smoking and SIDS risk with adjustment for (among other variables) maternal smoking during pregnancy and breastfeeding.

4. Comment: The conclusions in the document regarding breast feeding and SIDS risk in the Klonoff-Cohen *et al*. study is not justified given the large confidence interval.

Response: The document states only that no protective effect for SIDS was observed for breast feeding among the smokers (in contrast to the nonsmokers) and is consistent with the conclusions stated by the study's authors, although it was noted that the sample size among this particular group is small.

5. Comment: The commenter states that, like other dismissed studies, Mitchell *et al*. (1993) also presents data for women who actively smoked.

Response: The fact that the study population contains mothers who actively smoked has been noted in the document. This study is of interest, however, because it also presented data which suggest a significant relationship when the data are adjusted for maternal active smoking.

6. Comment: The "multivariate" maternal odds ratio of 1.65 presented by Mitchell *et al*. (1993) was misinterpreted and is actually an odds ratio for pre- and postnatal maternal smoking.

Response: The odds ratio described in the Mitchell *et al.* (1993) study was generated because of the possible relationship of smoking behavior between parents. The adjusted "multivariate" odds ratio of 1.65 was generated by controlling for many variables including, but not limited to, maternal smoking in pregnancy.

7. Comment: Mitchell *et al*. (1993) shows an overall absence of dose-response and no risk elevation when attention was restricted to nonsmoking mothers.

Response: These statements are consistent with those presented in the document. The study does, however, show a significant association between postnatal maternal smoking and SIDS after adjustment for smoking during pregnancy and other covariates and is also extensive in its examination of paternal smoking.

8. Comment: The commenter notes the possibility that the reported elevated risk in the Schoendorf and Kiely (1992) study could have been due to maternal active smoking early in pregnancy or ETS exposure.

Response: This possibility has been noted in the document.

9. Comment: The Nicholl and Cathain (1992) study was not adjusted for potential confounders.

Response: This fact has been noted in the document.

**Raphael and Philip Witorsch of the Center for Environmental Health and Human Toxicology, Washington, DC, for the Tobacco Institute**

1. Comment: SIDS "In spite of the intriguing data [in the Klonoff-Cohen *et al*. study], this paper has several aspects of concern." "[A]fter birth there are only 56 cases and 24 controls from smoking mothers, a relatively small sample for this critical subset." "Thus, judgments made by OEHHA may have been based upon a relatively small number of cases which may account for the very wide confidence intervals...for most ORs."

Response: The available cohort in the Klonoff-Cohen *et al.* (1995) study includes 200 SIDS cases and 200 controls. As the population is further divided into ETS exposure category subsets, the numbers become smaller. Although some of the reported 95% confidence intervals are large, the odd ratios from the associations of concern did not span unity. The population for which there were inadequate numbers to establish a clear relationship was that of smoking mothers who breastfed their infants. In this case, no protective effect was observed, although there is the possibility that such an effect would be observed in a larger population.

2. Comment: Among the elevated ORs when considering smoking in the same room, "none of these values appear to differ significantly from their respective baselines on the basis of their 95% CIs (Berry, 1986)." It is premature to consider ETS as a reproductive and developmental toxic agent on the basis of the association between such exposures postnatally and incidence of SIDS in offspring. No data exist indicating whether ETS exposure *in utero* is a risk factor for SIDS. The weight of evidence does not support the conclusion that there is sufficient evidence of an association between postnatal ETS exposure and SIDS in infants.

Response: On the basis of the available studies, including two recent studies (Klonoff-Cohen *et al.,* 1995; Blair *et al.*, 1996) which have now been summarized in Chapter 4, and two earlier studies (Mitchell *et al.*, 1993; Schoendorf and Kiely, 1992), one can conclude that ETS exposure is an independent risk factor for SIDS. In conjunction with the association of ETS exposure with SIDS risk, several investigators have observed dose-response relationships between number of cigarettes smoked during pregnancy and SIDS risk. Sources of ETS exposure in the studies have included maternal smoking after pregnancy, paternal smoking, household smoking, and smoking during different seasons. Limited corroborative evidence has been found showing high incidence of elevated cotinine in pericardial fluid of autopsied SIDS cases (Milerad *et al.*, 1994).

3. Comment: "Other recognized risk factors for SIDS have not been addressed in the relevant studies noted above, such as areas of residence (rural vs. suburb), day of the week, mobility of the household, house heating, room where infant slept, room ventilation, and density of individuals of household (McGlashan, 1989)." "Since...the mechanisms involved in the etiology of SIDS have yet to be defined..., these considerations are particularly important."

Response: The observations made in the recent studies (Klonoff-Cohen *et al.,* 1995 and Blair *et al.*, 1996) indicate that one of the more important risk factors for SIDS has been identified, and it is exposure to environmental tobacco smoke. Clearly, other risk factors exist and many have been controlled for in the studies described in the document.

4. Comment: Cognition and Behavior "In our opinion the conclusion by OEHHA that the weight of evidence is suggestive of an association between ETS exposure and cognition and behavior is premature and should more appropriately be regarded as inadequate."

Response: Four fairly well-controlled studies showed modest decrements associated with ETS exposure while one did not. Clearly additional work is needed to confirm these suggestive findings.

**Richard A. Carchman of Philip Morris**

1. Comment: The McGlashan study should be eliminated as the only data presented from it is a risk estimate for both forms of maternal smoking (maternal active smoking during and after pregnancy combined).

Response: As stated in the document, the nature of this study, with extensive overlap between women smoking during and after pregnancy, precludes the clear identification of an independent relationship for ETS exposure (in the absence of *in utero* exposure). It has been included because it is among those attempting to examine the relationship between ETS exposure and SIDS. Its authors state that their study shows cases (unexplained infant deaths) were more likely than controls to have a father who smoked, although these data were not presented.

2. Comment: The summary of the SIDS study by Bergman and Wiesner (1976) "cites risk estimates for maternal smoking during and after pregnancy, when only the latter is relevant to a discussion of ETS exposure."

Response: As with the McGlashan study (see above) the extensive overlap between women smoking during and after pregnancy precludes identifying an independent relationship for ETS exposure. The crude odds ratios presented in the summary were included for informational and comparative purposes.

3. Comment: The commenter has concerns with the statement in the Review Draft that the "main limitations" of the available studies is "the lack of a paternal smoking effect in families with non-smoking mothers (seen in Mitchell *et al*., 1993)", and asserts that this is not a limitation, but the most useful data.

Response: The concluding paragraph of the section on ETS and SIDS has been updated to include new studies which have been added to the section (i.e., the Klonoff-Cohen *et al.* and Blair *et al.* studies). The statement regarding the limitations of the "existing" studies has been deleted.

4. Comment: "The Review Draft fails to discuss recent reports suggesting that the prone sleeping position may be an important risk factor for SIDS."

Response: The introduction to the section on SIDS acknowledges that sleeping in the prone position is a risk factor for SIDS. The data and analyses from the Mitchell *et al.* (1993) and the Klonoff-Cohen *et al.* (1995) studies account for sleeping position.

5. Comment: The Review Draft's discussion of SIDS does not provide a sufficient review of the uncertainties associated with defining and diagnosing this condition."

Response: The document defines SIDS as "the sudden death of any infant which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death (Beckwith, 1970)." The definition itself speaks to the uncertainty in identifying SIDS cases. For a more complete discussion of the issue, the reader is referred to the cited review.

6. Comment: There was inadequate discussion of the flaws of the Klonoff-Cohen *et al* study.

Response: The ETS document has been updated to include a summary of the Klonoff-Cohen *et al.*, 1995 study, including its limitations.

**Jennifer Jinot of the U.S. EPA**
Numerous minor editorial changes were made to the document in response to comments which were provided on a marked-up copy.

1. Comment: "With the inclusion of the Klonoff-Cohen study, I agree with the conclusion that there is sufficient evidence that postnatal exposure of the child is an independent risk factor for SIDS." Change the statement that "a causal relationship between postnatal ETS exposure and SIDS" given that the causes of SIDS are, by definition, unknown.

Response: The term 'causal', in this case, indicates that the evidence from the numerous studies has shown that ETS exposure is a risk factor for SIDS. We acknowledge that the etiology of SIDS is not fully understood, although plausible hypotheses have been put forward.

2. Comment: Separate the seven studies summarized, as the first three (Bergman and Wiesner, 1976; McGlashan, 1989; Mitchell *et al.*, 1991) do not control for maternal smoking during pregnancy.

Response: The available studies (which have now increased in number to ten) have been presented in chronological order and represent the body of literature available in the evaluation postnatal ETS exposure and SIDS. As it happens, the three earliest of the studies are those which do not control for maternal smoking during pregnancy, and thus comprise a grouping of sorts. However, inclusion of the entire set of studies in the section gives some indication of the impact of controlling for maternal smoking on the outcome.

3. Comment: Consider renaming the second exposure category in Table 4.1 (Schoendorf and Kiely) "MS after pregnancy only vs. no MS".

Response: For consistency within the document, the exposure category headings in Table 4.1 have not been modified, although this point of clarification has been noted.

**Steven Bayard of the U.S. EPA**

Comment: Consider changing the weight of evidence classification for Postnatal Physical Development from null to inadequate based on the positive evidence that active smoking during pregnancy causes some postnatal growth retardation, given the six studies (three data sets) in Table 4.4 each show a small decrement in growth with ETS exposure. "...[U]nless the author can show that these studies were of 'high quality' and the observed decrement 'is probably no effect of concern', then the evidence should be characterized as inadequate".

Response: The document now indicates that there is little to no epidemiological evidence that ETS exposure has a significant effect on the height growth of children.

**T.A. Slotkin of Duke University**

1. Comment: Consider adding a recent paper (Slotkin *et al*., "Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome", *Brain Research Bulletin*, in press) which demonstrates that prenatal nicotine exposure in rats compromises the ability of the animals to survive hypoxia after birth.

Response: A summary of this study (citing the now published version: *Brain Res Bull* **38**(1):69-75) has been added in the section of the document entitled "Animal Studies of SIDS and Tobacco Smoke Exposure" (Section 4.2.3).

2. Comment: The section which identifies the mechanism should be updated to include those data which suggest that fetal hypoxia/ischemia is not the only mechanism underlying developmental toxicity and that other effects such as CNS stimulation and mitotic arrest in brain cells may be involved (the commenter refers to his papers, "Development of [$^3$H]nicotine binding sites in brain regions of rats exposed to nicotine prenatally via maternal injections or infusions"; "Effects of prenatal nicotine exposure on biochemical development of rat brain regions: maternal drug infusions via osmotic minipumps"; and those of Navarro *et al*., "Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth", *Brain Res Bull* **23**:187-192, 1989; McFarland *et al*., "Inhibition of DNA synthesis in neonatal rat brain regions caused by acute nicotine administration", *Dev Brain Res* **58**:223-9, 1991). An implication of this is that nicotine delivery methods other than smoking (smokeless tobacco products, nicotine patches) which may not produce hypoxia/ischemia still leave the fetus at risk.

Response: The discussion of the mechanism of action has been revised to acknowledge the support that animal studies have provided in this area. The wording in the document leaves open the possibility that mechanisms other than hypoxia may be responsible for developmental toxicity.

**Peter Fried of Carleton University, Ottawa, Ontario**

Comment: The overview of maternal active smoking and postnatal physical development and the summary of these findings is too strong. Some of the studies cited as providing evidence for such effects reported that their observations were non-significant and work in 1992 by Day, Cornelius *et al*. (*NeurotoxTeratol,* 1992, **14**:407-414), which was not cited, failed to find postnatal growth effects. Other labs (*e.g.* Streissguth) have also reported no effects after 8 months of age. More recent work (*e.g.*, Day, 1994; Conter, 1995) also failed to find effects.

Response: The Executive Summary and elsewhere notes that there is no evidence that postnatal ETS exposure has a significant impact on height growth. In determining whether an adverse effect may be associated with ETS exposure, an effort has been made to emphasize the analyses of studies with ETS exposure and any appropriate and supportive evidence from studies in experimental animals. The review of adverse effects from maternal active smoking has been limited.

## Male and Female Reproductive Effects

**P.N. Lee, for the Tobacco Institute**

1. Comment: Relevant Evidence. Theoretically, effects of paternal smoking may be those which arise from the effect of active smoking on sperm which is "a mechanism having nothing to do with ETS exposure".

Response: This valid point of concern is discussed in the revised document; Section 5.4.4.

2. Comment: Fertility. The commenter notes several studies in which ETS exposure is associated with increased fertility (Tokuhata, 1968; Wilcox *et al*., 1989; Weinberg *et al*., 1989; Florack *et al*., 1994; Dunphy *et al*, 1991), but also notes some of the shortcomings of the studies.

Response: These studies (except for Dunphy *et al.*, 1991) are summarized in the text and tables for Chapter 5 of the revised document. The paper by Dunphy *et al*. (1991), which concluded there was no effect of smoking on fertility outcomes in couples attending a fertility clinic, was not included in the document because it did not contain any actual data and because there were no apparent attempts to account for any confounding factors.

3. Comment: One other study (Dunphy *et al.*, 1991) has studied the relationship of infertility to husband's smoking."

Response: The report by Dunphy *et al*. (1991) was a description of fertility outcomes in couples attending a fertility clinic. Confounding factors (e.g., age of the subjects) were not addressed, nor were any actual data presented. For these reasons, the report did not present any useful information for the document.

4. Comment: The evidence relating to maternal smoking during pregnancy has been inappropriately described in the section heading as relating to ETS exposure *in utero*.

Response: The discussion of the Wilcox *et al.* (1989) study includes mention of *in utero* exposures for comparison with the effects of childhood ETS exposures other than *in utero*. The document does not consider *in utero* exposure from maternal smoking to be ETS exposure.

5. Comment: Taking all three sets of evidence together [Baird and Wilcox, 1985; Suonio *et al*., 1990; Olsen, 1991], there is clearly little indication of an adverse effect of ETS exposure on fertility and fecundability. Indeed there are as many, if not more, associations which suggest a beneficial as an adverse effect.

Response: The conclusions reached in the document indicate that there are inadequate data upon which to determine whether there is an association between ETS exposure and effects on fertility or fecundability.

6. Comment: "[N]o reference is made to the recent review by Baird (1992) which considers epidemiological data for some 16 studies..." in Section 5.2.1. "I believe the evidence on active smoking should be put over more tentatively, along the lines of the Baird (1992) review."

Response: The document considers several review articles, and is comprehensive in its coverage of original data. Inclusion of additional reviews would be of limited value.

7. Comment: Age at Menopause I agree with the Review Draft that the data presented in Section 5.3 are inadequate to determine whether ETS exposure is associated with a lower age at menopause.

Response: Comment noted.

8. Comment: Male Reproductive Toxicity. The Review Draft should cite the reservations of the authors of the Vine *et al*. (1994) study which states that "Although cigarette smoking is associated with a reduction in sperm density, cigarette smoking may not be the cause of the reduction. It is possible that some other factor(s) associated with cigarette smoking may actually cause the decrease in sperm density among smokers. Smokers are, for example, more likely than nonsmokers to take drugs and medications, consume caffeine and alcohol, experience sex earlier, and divorce".

Response: The document states in Section 5.4.2 that no studies were found that were designed to examine the association between ETS exposure and altered male fertility parameters. Confounders were often unaccounted for, as stated in the document. In light of these conditional statements already present in the document, the remarks by Vine *et al*. (1994), mentioned by the commenter, are unnecessary.

## RESPIRATORY HEALTH EFFECTS

**Jennifer Jinot of the U.S. EPA**
1. Comment: Some of the medical terms could be redefined for a broader audience.

Response: In updating the document, OEHHA staff tried to make the report more accessible by defining medical terms when they were first used and again as needed throughout the text.

2. Comment: The commenter believes that OEHHA staff mischaracterized the conclusions articulated by the U.S. EPA in its 1992 monograph on passive smoking regarding the extent of the causal relationship between ETS exposure and childhood asthma. The commenter cited the following language from the earlier draft, "Though the U.S. EPA was unwilling to definitively characterize as causal the association of ETS and induction of asthma, that organization nevertheless assumed a causal relationship in order to derive a quantitative estimate of risk."

Response: In revising the document, OEHHA staff deleted the language of concern to the commenter, and re-cast the sentence as follows: "The U.S. EPA derived a quantitative estimate of risk of asthma induction associated with maternal ETS exposure."

**Philip and Raphael Witorsch, for the Tobacco Institute**
These comments addressed the relationships between exposure to ETS and specific health outcomes noted in the OEHHA draft report. OEHHA staff responses are organized to follow the same format.

1. Comment: Asthma (Exacerbation)
The commenters believe that the published literature does not support the description of ETS exposure as a potential risk factor for exacerbations of asthma, citing selected results of several studies to support their position. They also state that "the data cited in the OEHHA report are incomplete and misleading".

Response The draft has been updated and includes more details on several earlier studies, in order to respond to the comment about our presentation of data as "incomplete". We do not agree that our presentation is "misleading"; the interested reader can assess the validity of this characterization by consulting the original literature. Re-evaluating this literature, including several studies published since the draft report was first circulated, reinforced the earlier concurrence with the U.S. EPA's statement that, "There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. (p. 248)". In addition, most, if not all, of the "controlled" studies of asthmatics exposed to ETS were reviewed. These studies suggest that there is a subpopulation of asthmatics who are especially susceptible to acute ETS exposure. These findings are summarized in the revised draft.

2. Comment: Respiratory Infections
The commenters state " We agree with the position of OEHHA that there is a consistent association between estimates of ETS exposure (usually maternal smoking) and respiratory infections in infants and toddlers, which diminishes in older (school-age) children...We disagree, however, that this consistency per se 'strengthens the inference of a causal association' and that 'most of these studies, while not free of all sources of bias, had adjusted for many identifiable confounding variables and found that ETS effects were independent of sex, race, maternal age, SES, residential crowding and number of siblings.'" The commenters then state that it is premature to conclude that ETS exposure causes increased respiratory infections in children because of various study design flaws, including misclassification of disease status, uncontrolled confounding and other factors.

Response: This section of the ETS report was based principally on a review of the reports by the Surgeon General (1986), the National Research Council (1986), and the U.S. EPA (1992), which conclude that a causal relationship is the most likely explanation of the consistently observed associations between ETS exposure and pediatric respiratory illness. The discussion of this issue was adequately addressed in these reports and OEHHA did not undertake a *de novo* analysis of the primary literature. The thrust of the comments is that all these earlier analyses were also premature in assigning a causal role to ETS.

The ETS draft document does not state that, by itself, the consistency of findings of an association between ETS exposure and childhood respiratory illness in dozens of studies justifies a causal inference. However, consistency of results among different studies with different designs and study populations is clearly one of several ingredients in the recipe for causation. In Table 2 of their review article, Witorsch and Witorsch (*Indoor Environ* 1993; 2: 71-91) indicate that 27 of the 41 studies considered at least 7 potentially confounding variables. This actually appears to support the statement in the ETS draft that "...most of the studies ... had adjusted for many identifiable confounding variables." Thus, it must be the second part of the statement (i.e., "ETS effects were independent of sex, race, maternal age, SES, residential crowding, and number of siblings") with which the commenters apparently do not concur. The basis for this disagreement seems to be that, short of a "perfect" series of studies (i.e., with validation of the health endpoints through a review of medical records, and the inclusion of up to 21 "potential confounders" in the analysis of each study), one cannot draw any conclusions about the independent effects of ETS exposure. The implication of this argument is that the conclusions presented in the reports by the Surgeon General, the National Research Council, the U.S EPA, and by extension, OEHHA, are all erroneous.

The commenters' methodological criticisms are not compelling. While validation of clinical outcomes by review of medical records reduces the likelihood of misclassification of disease status, in most instances such misclassification would have the effect of *reducing* the magnitude of the relationship between ETS exposure and pediatric respiratory disease. Nondifferential misclassification of disease status would produce a downwards bias in the estimate of an ETS effect. Systematic misclassification of disease status may result in either upwards or downwards bias of an ETS effect, depending on the circumstances. Thus, while it would be desirable to have

validation of the clinical endpoint, the absence of such information is, in general, likely to produce an *underestimate* of ETS effects.

In epidemiologic studies, a confounder is a factor or variable that is associated with both the disease outcome and with the exposure of interest (in this case, exposure to ETS), and can produce a distortion of the relationship (or lack thereof) between the exposure and the disease outcome. If data on such confounders are collected during the course of a given study, then the potentially distorting effects of the confounder can be "controlled for" statistically during the analysis. However, many of the "potential confounders" listed in an article cited by the commenters are not likely to be confounders at all, such as "dampness and cold", and "outdoor pollution." For variables such as these to be considered confounders, one would have to assume that they are distributed differently among children whose parents are smokers and those who are not. Moreover, inclusion of nearly two dozen "potentially confounding" variables in investigations of ETS-related effects, as advocated by the commenters, would not only be expensive, but methodologically unsound. In any given study, there are likely to be few potentially confounding exposures sufficiently important to control for. Inclusion of a long list of of such putative confounders is methodologically inappropriate and may affect the precision (and therefore the statistical significance) of the estimate of the relationship between ETS exposure and disease.

3. Comment: Asthma (Induction)
The commenters believe that the draft has overstated the evidence of an association between parental smoking and asthma incidence in children, citing one of their review articles which states that "only 5 of 21 papers that deal with this issue show a statistically significant association." They then discuss several aspects of two of these papers.

Response: There are far more than 21 papers that address the relationship between ETS exposure and asthma induction. Even so, several papers described in the "review" article co-authored by the commenters (Hood *et al*., *Indoor Environ* 1992; 1:19-35) as negative studies actually show a positive statistically significant association between ETS exposure and the prevalence of asthma. Since the initial ETS draft was circulated, several other reports that address this issue have been published, most of which tend to support the document's characterization of childhood ETS exposure as a risk factor for induction of asthma. We have since undertaken a formal meta-analysis of the ensemble of published studies on asthma induction and ETS exposure, a summary of which has been included in the revised draft. The results of the meta-analysis support the position previously articulated in the draft.

4. Comment: Chronic Respiratory Symptoms
The commenters believe that the statement that "epidemiologic studies have linked chronic domestic ETS exposure with recurrent symptoms of cough, wheeze and excess phlegm production in children" is not supported by the facts.

Response: In this instance, rather than re-invent the wheel in the ETS draft, the conclusions of the three previous national evaluations of this subject were reviewed, and their findings were incorporated in summary form. There are dozens of studies, involving tens of thousands of

children, that served as the basis for the conclusions reached by the NRC, the Surgeon General, and the U.S. EPA. The commenters list the same generic concerns as those discussed in their comments on Section 5.1.2. Please see responses to those comments.

5. Comment: Decreased Lung Development (Children)
The commenters disagree with statements in the ETS draft document to the effect that ETS exposure is associated with small decrements in children's lung function.

Response: At the time the original draft was released, the relationship of children's lung function to ETS exposure had been extensively reviewed in the three major national evaluations referred to above. Dozens of studies, involving approximately 77,000 children, were reviewed in those reports, whose conclusions were summarized in the ETS draft. An independent review of all the studies evaluated at the federal level was not undertaken to avoid wasting scarce resources duplicating work that appeared to have been adequately conducted at the federal level. Thus, the main objection raised by the commenters seems to be that the results of a number of reports appear to be "very inconsistent." In our summary, we noted this inconsistency, so the principal concern of the commenters seems to be one of emphasis only.

The draft was revised to include information from more recent investigations of the relationship of ETS exposure to children's lung function. Several studies suggest that the effects of ETS on children's lung development may be attributable in part to delayed effects of *in utero* exposure. While these results do not directly contradict the conclusions of the federal evaluations of ETS and children's lung development, they do imply that, at least for this outcome, the mechanisms may involve prenatal as well as postnatal exposures.

6. Comment: Atopy/ Atopic Dermatitis
The commenters suggest that there is little evidence that ETS exposure causes children to become atopic (*i.e.*, to have a predisposition to develop allergies) or that atopic children are particularly sensitive to the adverse effects of ETS.

Response: Additional literature on these topics was reviewed. It was concluded that, "whether there is a relationship between the development of atopy and pre-natal or post-natal exposure to ETS has not been as thoroughly researched as have other outcomes discussed in this report. Published investigations of this issue have produced mixed results." The prior version had not included an explicit summary statement to this effect.

7. Comment: Cystic Fibrosis
The commenters critique three studies on ETS exposure among individuals with cystic fibrosis (CF) cited in the earlier draft report, and assert that "the evidence suggesting that children with ... cystic fibrosis are particularly sensitive to ETS is not compelling."

Response: These three papers and two others published recently were carefully re-evaluated. It was concluded that, "although several reports suggest that passive smoke exposure can affect patients with CF, the extent and magnitude of such effects are still uncertain. The evidence for an effect on hospitalizations is compelling, while the studies are less conclusive in showing an effect on pulmonary function or disease severity. The two studies that have looked at growth

have both found an inverse relationship between ETS exposure and linear growth." The basis for these conclusions is spelled out in the revised report.

8. Comment: Otitis Media
The commenters believe that OEHHA mischaracterizes the relevant literature by indicating that there is consistency of association between ETS exposure and middle ear disease in children. An updated analysis of that literature reveals that only 10 of 24 papers report a statistically significant association. In addition, OEHHA's suggestion of the plausibility of a biological mechanism for an association between ETS exposure and middle ear disease, for which evidence is virtually nonexistent, is speculative.

Response: See response to individual comments.

8A. Comment: The OEHHA report states that 10 of 12 studies reveal statistically significant relationships between ETS exposure and otitis media and/or middle ear effusions in children (p.5, paragraph 1). These studies are listed in Table 5.1 of the OEHHA report and were reviewed either in the reports of the Surgeon General (1986), National research Council (NRC) (1986) or the U.S. EPA (1992). An analysis of the literature that we performed (Hood et al., 1992), which includes 8 studies listed in Table 5.1 and an additional 9 studies not so listed, indicates a considerably different situation, namely, a statistically significant relationship between parental smoking and middle ear disease in only 6 of 17 studies (Table 3 of Hood et al., 1992).

Response: The Tobacco Institute-sponsored study alluded to above (Hood et al., 1992) reviewed only 8 of the 12 otitis media studies critiqued by the Surgeon General's office, National Research Council, or US EPA. The Hood review erroneously reported that Pukander et al.'s study showed no significant relationship between parental smoking and otitis media (chi-square for trend for number of acute otitis media attacks vs. parental smoking: 10.68, df=1, p=0.001 - see attached calculations). Two of the "negative" studies cited in the Hood review (Marchisio et al., 1988 and Rockley, 1988) were published in an edited work, but did not appear in peer-reviewed journals; they will not be further considered here. Hood et al. also included a study of respiratory illness as a function of indoor temperature and humidity which only incidentally addressed the issue of parental smoking (Ross et al., 1990). The relationship between parental smoking and otitis media in this study was presumably encompassed under the analysis of "socio-demographic factors," although direct numbers pertaining to this relationship were not presented.

8B. Comment: Several items listed in Table 5.1 of the OEHHA report are either in error or misleading. The table indicates that Hinton (1989) reports a statistically significant association between parental smoking and middle ear disease. This is incorrect. None of the associations in this paper had a $p<0.05$.

Response: The commenter is correct with reference to the Hinton paper. OEHHA staff had performed a chi-square calculation for trend comparing controls to "other ENT patients" to tympanostomy patients. Entry of an erroneous cell value resulted in a "significant" p value ($p = 0.03$), whereas the correct entry yield a "borderline" significant value (0.06).

8C. Comment: The statement in Table 5.1, pertaining to the paper by Tainio et al. (1988), that ETS is a risk factor for otitis media (OM) is misleading. The RR listed in the Table appears to be that obtained form univariate analysis. When considered among 17 potential confounding variables, parental smoking was found not to be statistically significant risk factor for recurrent OM during the first 2 years and it is stated in the paper that parental smoking is not a risk factor for recurrent OM.

Response: Tainio et al. defined ROM ("recurrent otitis media") as "...five or more separate episodes of otitis media (OM) during the first 2 yr of life or four such episodes during their 2nd yr." Although the authors state: "Parental smoking was more frequent among the infants with ROM than in the comparison group (54 versus 33%; $p < 0.05$)," parental smoking was apparently not considered a significant risk factor for ROM in a stepwise logistic regression analysis (Table 1). However, smoking by one or both parents was a significant risk factor for three or more episodes of otitis media during the first two years of life, an equally valid outcome measure (Table 2: RR=1.7; 95% CI=1.1,2.7).

8D. Comment: The findings of Teele et al. (1989) also deserve comment. While a statistically significant association between parental smoking and acute OM is demonstrable during the first year of life, it is noteworthy that this is not the case for the 3 year cohort and 7 year cohort.

Response: This point was already adequately dealt with in Table 5.1.

8E. Comment: The OEHHA document indicates that two of the studies, those of Strachan et al. (1989) and Etzel et al. (1992) used objective measures for ETS exposure (salivary and serum cotinine levels). This is a misleading representation of the literature. While the study of Strachan et al. (1989) shows a statistical correlation between salivary cotinine and abnormal tympanometric findings (type B) indicative of middle ear effusion, subsequent studies from the same laboratory are inconsistent with this. Strachan (1990) reported no statistically significant correlation between the number of smokers in the household and type B tympanograms after multiple logistic regression for a variety of confounding variable. In another study, this group reported a lack of correlation between salivary cotinine level and "ear trouble" (Strachan et al., 1990).

Response: Neither of the two citations referenced above are directly comparable to Strachan's 1989 study. Strachan (1990) used number of adult smokers in the home - rather than salivary cotinine - to explain tympanometric findings. Strachan et al. (1990), which focused on chest symptoms rather than otitis media, used the subjective parental report of "ear trouble" - not tympanometry - as an outcome measure. Despite the fact that control for "housing tenure, domestic crowding, gas cooking and damp walls" in a multiple logistic regression analysis resulted in a loss of significance in the relationship between reported parental smoking and abnormal tympanograms (odds ratio 1.8, 95% CI = 0.96-3.40), Strachan (1990) summarized: "Parental smoking was an important determinant of middle ear underpressure and effusion." Because non-differential misclassification biases studies toward the null, neither of these two studies would be expected to have the precision and power of Strachan (1989), which used objective measures for both ETS exposure and middle ear pathology.

8F. Comment: The study of Etzel et al. (1992), as well as that of Teele et al. (1989), do not rule out the possibility that the effect an association attributed by ETS is mediated by an in utero route.

Response: Very few epidemiologic studies have sufficient numbers of subjects to permit a separate analysis of the children of women who smoked vs. those who didn't smoke during pregnancy. Assuming such a stratification could be made, a further distinction would need to be made between the offspring of nonsmoking women exposed or unexposed to ETS during pregnancy. This scheme would actually result in six exposure strata. Further, in order for this factor to constitute a potential confounder, intrauterine ETS exposure would need to be associated with both postnatal ETS exposure status and with the endpoint of interest (i.e., otitis media). The likelihood that multiple studies show an association between ETS exposure in childhood and OM as a consequence of such an artifact is, in the judgment of OEHHA staff, very low.

8G. Comment: Table 5.2 of the OEHHA lists an additional 6 epidemiologist studies that were not include in the Surgeon General, NRC and EPA reports. Five of the 6 papers on this list failed to show a statistical relationship between parental smoking and middle ear effusion. The OEHHA takes the position that "several of these studies were problematic with respect to their study designs". This may well be the case. However, they are no more problematic than those listed in Table 5.1, as noted above.

Response: Per the original text, OEHHA staff disagree with the commenter's assertion that, as a whole, the studies referenced in Table 5.2 were as well-designed and executed as those referenced in Table 5.1.

8H. Comment: The most objective way to evaluate the literature relating parental smoking and middle ear disease in children is to consider all of the available studies on this issue (i.e., those listed in Table 3 of Hood et al., 1989, as well as the 7 additional papers listed in Tables 5.1 and 5.2 of the OEHHA report (Tainio et al., 1988; Teele et al., 1989; Takasaka et al., 1990; Etzel et al., 1992; Barr and Coatesworth, 1991; Green and Cooper, 1991; and Ponka et al., 1991). In this composite list of 24 papers, only 10 report a statistically significant association between outcome and parental smoking (using a very liberal interpretation of what constitutes a statistically significant association). This would hardly support the statement that "epidemiology data strongly support a relationship between ETS exposure in the home and either acute otitis media with effusing or serious otitis media".

Response: The studies with the most rigorous definitions of exposure and outcome (Etzel, 1992 and Strachan, 1989) showed unequivocal associations between ETS exposure and otitis media in children. As noted above, some studies of the so-called "negative" studies referred to in a Tobacco Institute-sponsored review: 1) under-utilized their own data by not analyzing for trend (Pukander et al., 1985; Hinton, 1989); 2) showed significant relationships that became only borderline after adjustment for multiple co-factors (with consequent loss of statistical power to demonstrate the principal effect- Tainio et al., 1988); and 3) are essentially uninterpretable

because of either their non-peer-reviewed status or inadequate detail in reporting results (e.g., Ross, Marchisio, and Rockley). None of these studies showed a protective effect of ETS for otitis media. Were it not for the diversity of study designs, these studies could be combined in a formal quantitative meta-analysis. Short of such an exercise, it is the judgment of OEHHA staff that the preponderance of the epidemiological evidence points to a causal role for ETS in the genesis of otitis media, particularly in young children. In this latter regard, OEHHA staff concur with opinions expressed in the United States Environmental Protection Agency report (1992).

8I. Comment: The OEHHA report also attempts to support the argument that ETS causes middle ear disease on the basis of existence a plausible biological mechanism for such a relationship. The contentions that ETS decreases mucociliary clearance and decreases eustachian tube patency due to mucosal swelling are based only on data in active smokers, a situation that, from a toxicological point of view, is quite different, both qualitatively and quantitatively, from ETS exposure.

Response: As is stated clearly in the text, empiric observations of decreased mucociliary clearance pertain to the tracheobronchial tree of active smokers. However, observations of acute upper airway mucosal swelling, as documented in experiments by Bascom and co-workers, are among non-smokers acutely exposed to ETS.

8J. Comment: The OEHHA document also contends that decreased patency and impaired mucociliary clearance are secondary to increased frequency of viral upper respiratory tract infections (URI's) resulting from ETS exposure. It cites Fleming et al. (1987) to support this position. This citation is at best only partially supportive, since these authors report that maternal smoking, which is statistically associated with URI's, is not significantly associated with otitis media.

Response: The commenter is correct in pointing out that the risk of OM as a function of maternal smoking in the Fleming study was only 1.1. However, most investigators would consider maternal smoking alone as an inadequate index of ETS exposure.

8K. Comment: The OEHHA document contends, furthermore, that ETS induces adenoidal hyperplasia can decrease eustachian tube patency. The papers cited to support this position are quite weak. Said et al. (1978) do not verify the endpoints (adenoidectomy and tonsillectomy) by physician examination or medical records. These endpoints were obtained from questionnaires completed by the subjects (10-20 years of age) and without parental verification. In addition, relatively few confounders were considered in this study (such as age, gender, day care, sibling size and history of appendectomy). Omitted from such consideration were such factors as family health history and active smoking. It was not clear from this study how confounder adjustments were made. This study also reported an association between maternal smoking and appendectomy, which suggests some nonspecific association between maternal smoking and the endpoint (e.g., predisposition toward surgery or general health of the subject). Corbo et al., (1989) do not report an association between parental smoking and adenoids and tonsillectomy and only one between parental smoking and snoring, which may, in some way, be related to enlarged adenoids and tonsillectomy.

Response:Although most individuals know whether or not they have had a tonsillectomy and adenoidectomy (T&A), the commenter is correct in pointing out that, ideally, medical records should have been reviewed for the Said study. Likewise, a history of snoring is, indeed, an indirect index of adenoidal hyperplasia, although it was, in turn, related to previous T&A in the study in question (Corbo, 1989). We are indebted to the reviewer for the suggestion that ETS exposure may be associated with general health status. One should also note that ETS exposure is related to increased circulating IgE levels in children, another index of immunologic activation.

8M. Comment: Finally, the attempts to estimate attributable risk of ETS exposure to otitis media are inappropriate, since the foregoing discussion indicates that such associations are inconsistent.

Response: In the opinion of OEHHA staff, characterization of the link between ETS exposure and OM as "inconsistent" is a biased interpretation of the literature. The link is of sufficient strength and consistency to allow meaningful dose-response observations and attributable risk calculations.

# CARCINOGENIC EFFECTS

## Lung Cancer

**Larry Hedges of the Department of Education, University of Chicago, for Phillip Morris**
1. Comment: The U.S. EPA 1992 meta-analysis of 11 studies, conducted in the U.S., of the effect of ETS should have used a random effects model instead of the fixed effects model. "Thus fixed effects models can be considered a special case of the random effects model in which the variance component is assumed to be zero."

Response: A test for homogeneity of variance for the 11 U.S. studies was statistically nonsignificant; this supports the use of the fixed effects model. The U.S. EPA metaanalyses were done separately by country because preliminary results indicated that the results differed among countries.

2. Comment: U.S. EPA did not correct for publication bias. In this case, studies indicating an increase in lung cancer with ETS exposure are more likely to be submitted and published than are studies not showing an increase. If publication bias is corrected for in those 11 studies, the resulting "elevated risk is not statistically reliable."

Response: Possible publication bias in ETS-lung cancer studies has been examined many times and found to be without merit. Bero *et al*. (1994), cited in the References to Chapter 7, recently addressed the topic. Because of the importance and interest in this subject any large, well-designed study is likely to be published whether it is positive or not.

3. Comment: The Fontham *et al*. (1994) study, published after the release of the U.S. EPA report in 1992 is a completion of the Fontham *et al*. (1991) study which was reviewed by U.S. EPA. The ETS document should indicate this characterization in its assessment.

Reponse: Section 7.2.2 notes that preliminary findings from the U.S. multicenter study, published as Fontham *et al*. (1991) were included in the U.S. EPA 1992 document.

**Stanley M. Greenfield, Scottsdale, AZ**
Comment: The ETS document is quite good. The analyses of ETS and lung cancer fail to consider the confounding effects of other airborne carcinogens. He notes the recent data by Dockery and others on excess mortality due to ambient pollution (especially particulates) and believes that this "source" should be accounted for in any determination of a stratified response to ETS. Since this has not been done, he questions the results.

Response: The important confounders and their effects on the overall assessment were carefully considered in the analyses.

**Lawrence B. Gratt of IWG Corporation and Willard R. Chappell of the Department of Environmental Science, University of Colorado at Denver**

1. Comment: When the four U.S. studies on ETS and lung cancer published since 1992 are added to U.S. EPA's meta-analysis, the results of the meta-analysis are statistically nonsignificant.

Response: After including the four more recent U.S. studies in the meta-analysis, Kenneth Brown, a co-author of the 1992 U.S. EPA report, calculated a pooled result of 1.09 with a 90% confidence interval of 0.99-1.20, just shy of statistical significance at the $p = 0.05$ level. Results from other update analyses done by the same investigator for a submission to federal OSHA for its evaluation of ETS were statistically significant. In 1992 Brown had concluded that ETS could be considered a U.S. EPA known human carcinogen (Group A). In his 1995 submission to OSHA Brown concluded: "Based on the assessment of all the evidence of this report and in accordance with accepted guidelines and the causality criteria listed above for interpretation of human data, this report concludes that ETS is a carcinogen. Exposure of nonsmokers increases their risk of developing lung cancer." The U.S. EPA analysis depended on a total weight of evidence approach, not just the one adjusted odds ratio from one meta-analysis of 11 U.S. studies on the relationship of ETS and human lung cancer cited by the commenters. Many other analyses including dose-response analyses, highest exposure group analyses, adjustments and other analyses for biases and confounders, and an extensive evaluation of all the epidemiologic data were included. Groups from six countries, not just the 11 U.S. studies, were addressed in the evaluation.

2. Comment: A meta-analysis of workplace exposure to ETS and lung cancer conducted by the commenters showed a pooled odds ratio of 1.06 which is statistically nonsignificant.

Response: Taken together the studies of spousal exposure to ETS and lung cancer provide are more informative than the workplace studies. There are two concerns with the commenters' meta-analysis of workplace ETS. First, the workplace meta-analysis combines U.S. studies with non U.S. studies, but the metaanalyses of lung cancer in spouses of smokers are calculated only within a country. Thus comparability of the approaches is a problem. The greater concern is that the commenters' meta-analysis uses a final relative weight of 49% for the Janerich *et al*. (1990)/Varela (1987) study, which is approximately twice the combined weight assigned the 2 largest U.S. studies (Brownson *et al.*, 1992; Fontham *et al.,* 1994). The matched pairs analysis study design of Janerich/Varela apparently leads to this excessive weighting; however, a qualitative analysis of the data indicates that these weights misrepresent the overall confidence in the studies. The Janerich/Varela analysis should be reviewed by the commenters to determine whether the individual matching was preserved or at least post-stratified or adjusted for spousal exposure.

**William J. Butler of Environmental Risk Analysis, for R.J. Reynolds**

Comment: New analyses of the studies by Brownson *et al.* (1992) and Fontham *et al.* (1994) were conducted by the commenter at the request of R.J. Reynolds Tobacco Company. Brownson *et al.* (1992) and Fontham *et al.* (1994) analyzed their data improperly. Had their data been analyzed properly, they would have found no association between ETS exposure and lung cancer.

Response: It is difficult to comment on the new analysis, which is unpublished and does not provide sufficient detail for evaluation. The recent analyses being criticized were conducted by two different teams of experienced epidemiologists, and were peer reviewed and published in well-respected journals, one in the *American Journal of Public Health* and one in the *Journal of the American Medical Association.*

**Gio Batta Gori of the Health Policy Center, for the Tobacco Institute**

Comment: Comments were submitted by the Washington law firm of Covington and Burling. The portion of the comments which criticize the 1992 U.S. EPA report have also been published in two peer-reviewed journals, the *Journal of Clinical Epidemiology* (Science, policy and ethics: the case of environmental tobacco smoke, **47**:325-334, 1994 ) and *Risk Analysis* (Policy against science: the case of environmental tobacco smoke, **15**:15-22, 1995). The main points raised are: 1) The OEHHA draft accepts uncritically as valid the 1992 U.S. EPA risk estimates, from a U.S. EPA review based on *ad hoc* procedures and leading assumptions. 2) The U.S. EPA incorrectly presumes a similarity of mainstream smoke, side stream smoke, and ETS, yet "most components of side-stream-smoke (SSS) -- the main source of ETS -- become so diluted as to be undetectable by the most sophisticated analytical techniques." 3) U.S. EPA presumes that ETS has a greater potency than mainstream smoke. Prominent (unnamed) researchers in the field consider tobacco smoke a promoter rather than a direct carcinogen. This implies there is a threshold for carcinogenesis at the equivalent of 4-5 pre-1961 cigarettes per day for active smokers, the equivalent of which would never be attained for ETS exposure. 4) Since it may not be technically feasible to sufficiently control for all significant factors in a multifactorial process, "epidemiologic studies attempting to link ETS exposure and disease are doomed to produce the equivocal results reported in the literature." In fact, no available study on ETS and lung cancer has "adequately accounted for misclassification biases, exposure recall biases, interviewer biases, publication biases." Furthermore, many reviews, such as those of the U.S. EPA and OSHA, were selective in order to confirm preconceived expectations.

Response: Jennifer Jinot and Stephen Bayard of the U.S. EPA have published on the commenters remarks regarding the U.S. EPA 1992 report (Farland, Bayard, Jinot (1994). *J Clin Epidemiol* **47**:335-337; Jinot and Bayard (1994). *J Clin Epidemiol* **47**:339-349). Regarding the first point, the U.S. EPA analysis underwent extensive public scrutiny and external scientific peer review, and the general conclusions reached regarding the relationship between lung cancer and exposure to ETS are consistent with other authoritative reviews by the National Research Council and the Surgeon General. Regarding the second point, the exposure of active smokers differs from that of the ETS-exposed quantitatively, but not qualitatively. This is considered and addressed throughout the current OEHHA ETS document, including Chapter 7 on carcinogenic effects. A variety of exposure measurements indicate that exposure of non-smokers to ETS constituents is not insignificant. This issue is evident throughout the document. Regarding the third point, tobacco smoke, which is classified by the International Agency for Research on Cancer as a known human carcinogen, contains a variety of chemicals associated with various stages of the carcinogenic process, including early and late stages. Tobacco smoke contains many constituents identified individually as known human carcinogens (*e.g.*, cadmium, nickel, benzene, radionuclides), as well as PAHs that are present in other mixtures which are known human carcinogens. Regarding the fourth point, Chapter 7 discusses the relative merits of the most

recent epidemiological studies, for example, with regard to confounders and study size. Problems of conducting epidemiological studies on diseases such as lung cancer and etiological agents associated with low relative risks are well recognized. Issues related to these problems were carefully considered in the OEHHA draft, as well as in the earlier reports by U.S. EPA, the National Research Council, and the Surgeon General.

**Covington and Burling, attorneys for the Tobacco Institute**
Comment: The four main issues raised in divisions of a submitted document were: 1) Cal/EPA's ETS assessment is not cost effective. 2) Cal/EPA has incorrectly concluded that ETS poses a risk of lung cancer. 3) New studies further undermine Cal/EPA's conclusion that ETS poses a risk of heart disease. 4) New studies demonstrate that nonsmoker exposure to ETS is minimal.

Response: The package distilled the comments by consultants Peter N. Lee, Maurice E. LeVois, Maxwell W. Layard, and Gio B. Gori. Points 2, 3 and 4 are addressed elsewhere in these responses to comments. There were additional detailed points made under 1) including A) OEHHA is revising its risk assessment procedures; B) Cal/EPA must conduct its own independent assessment of the relevant scientific evidence; C) Cal/EPA must revise its ETS risk assessment to account for new information; and D) Cal/EPA's risk assessment will serve no regulatory purpose.

In regard to A), the document relies primarily on epidemiological evidence and would be unaffected by the contemplated changes in the evaluation of animal evidence for hazard identification and dose response data being contemplated at the federal and state level. In regard to (B), a review of Cal/EPA risk assessment procedures recently completed by the Risk Assessment Advisory Committee resulted in recommendations that Cal/EPA harmonize with U.S. EPA risk assessments when possible. An independent review by Cal/EPA would be contrary to this recommendation and not cost effective. In regard to (C), new information has been taken into account; this is outlined in the preface to the document. In regard to (D), this endeavor is a risk assessment for ETS. Regarding risk management activities, the document will be referred to the Department of Health Services for review. That Department handles tobacco control programs for California.

**James Wilson, of Cal/EPA Risk Assessment Advisory Committee, St. Louis, MO**
Comment: (Submitted comments on his personal letterhead as a mildly interested observer of the ETS controversy.) Cal/EPA should do a complete and fair reanalysis of the ETS and lung cancer connection rather than rely on the U.S. EPA 1992 analysis. The comments refer to two papers characterized as persuasive, one by Gross (*J Clin Epidemiol* **48**:587-598, 1995) which discusses problems with, and especially differences among, the 29 epidemiological studies used by U.S. EPA in its metaanalyses, differences which are "... large enough to make the meta-analysis susceptible to problems of confounding and bias that probably cannot be corrected." The second paper is a meta-analysis by Tweedie and Mengersen *(Statistics in Medicine* **14**:545-569, 1995) which presents dose-response analyses for pooled epidemiological studies on ETS.

Response: Aside from the meta-analysis performed by the U.S. EPA, the National Research Council, and Surgeon General committees evaluated the overall epidemiological evidence on

lung cancer and ETS exposure and came to a conclusion similar to that of the U.S. EPA, that the relationship is causal. The U.S. EPA meta-analysis was one of many factors considered by U.S. EPA in reaching its conclusion. Regarding the paper by Dr. Gross, similar arguments were presented by him on behalf of the Tobacco Institute to the U.S. EPA and its Scientific Advisory Board (SAB) and were considered in finalizing their report. On behalf of the Tobacco Institute, Dr. Tweedie also presented comments to the U.S. EPA on U.S. EPA's 1992 analysis of ETS. In their 1995 paper Tweedie and Mengersen used an ETS "cigarette equivalent" approach and estimated ETS risk based on the Darby and Pike model for active smoking and lung cancer. This was considered by both the U.S. EPA and its SAB, who declined to support its use in the U.S. EPA assessment (see Section 6.2.2 of the U.S. EPA report).

**R.L. Tweedie, Department of Statistics at Colorado University, for Phillip Morris**
Comment: The comments address consistency, combined analyses, publication bias, arguments concerning causality, and workplace exposure to ETS. Under consistency, the OEHHA assessment is criticized for calling the four recent ETS-lung cancer studies of spousal exposure "consistent" with those in the U.S. EPA analysis; they "are not really consistent, in the normal sense of the word, either among themselves or with the studies in the EPA report". There is a publication bias in the studies on ETS and lung cancer. To address combined analyses, the commenter and colleagues have carried out a new meta-analysis of the pooled U.S. results, which appeared in the journal *Lung Cancer* in March 1996. He finds that "after carrying out the correct meta-analysis of this data, -- the appropriate final estimate of RR based on the U.S. studies is at most 1.00-1.10." In regard to causality he uses the Bradford Hill criteria for causality to conclude "that there is a weak indication that this relationship is a causal one, but I strongly disagree with the statements on pp. 7 and 27 of the Review Draft, implying that the new studies reinforce the original conclusions of the EPA report or dispel any of the concerns about those conclusions." Finally, in regard to workplace exposure, he believes that no conclusion can be reached at present about workplace ETS exposure and lung cancer.

Response: With regard to the discussion of consistency, the OEHHA document has been modified. The pooled estimate of the new meta-analysis is not significantly different from that in the 1992 U.S. EPA report. Regarding Bradford Hill criteria for causality and dose-response, the U.S. EPA document and the OEHHA assessment conclude differently. The 1992 U.S. EPA report provides an extensive analysis of dose-response for the epidemiology studies. It found that, of the 14 studies with sufficient exposure information for testing dose-response relationships, "the proportion (10/14, $p<10^{-9}$) showing a statistically significant exposure-response trend is highly supportive of a causal association." The U.S. SAB concurred with U.S. EPA's dose-response analysis and conclusions. The issue of publication bias was addressed in the response to a comment above.

**Susan Rice, Susan A. Rice and Associates, Inc., for R.J. Reynolds**
Comment: The comments focus on animal data including the results of several studies of short-term exposure to "aged and diluted sidestream smoke (ADSS)" that were published since the 1992 U.S. EPA report. Some of her comments are quoted here directly. "The unique character of the complex mixture that is ETS makes extrapolation from mainstream smoke inappropriate." "The only way to evaluate the potential effects of the complex mixture known as ETS is to test

ETS." However, "aged and diluted sidestream smoke was developed as a surrogate for ETS." "Contrary to the U.S. EPA's assertion, a relationship between ETS exposure and lung cancer is not biologically plausible." Summaries of several animal studies are provided. The commenter concludes that Cal/EPA should consider the animal data and that these data do not suggest an association between ETS exposure and lung cancer.

Response: While some of the papers mentioned by the commenter present new data, animal studies suffer both from the inadequacy of animal inhalation models to reflect known human responses to tobacco exposure and from the potential for inadequate statistical power to observe a response with short-term exposures to low concentrations of toxicants. Some recent animal studies of short-term exposures to high levels of ADSS showing increased levels of DNA adducts and other signs of toxicity can be considered supporting evidence for carcinogenicity.

Animal studies generally suffer from the uses of small numbers of animals which are from genetically inbred research strains. The animal studies cited are of short duration (the longest cited study lasted six months), and do not follow protocols used for establishing carcinogenic effects. Because the studies are of insufficient duration and the testing of different strains and species is limited, they cannot be used to make conclusions regarding long-term exposure to ETS in the heterogeneous human population. It is of interest that one report cited, by Rajini and Witschi (1994), did find that two strains of mice responded differently to sidestream smoke, one indication of a heterogeneous response.

A relationship between ETS exposure and lung cancer is biologically plausible. The same carcinogens are present in ETS as in other cigarette smoke fractions; cigarette smoke is irritating to lung tissue; and exposure can be long-term. The 1995 paper of Witschi *et al*. cited by the commenter states: "There is high biological plausibility that ETS is a carcinogen. The same carcinogenic chemicals that can be found in cigarette mainstream smoke are present in ETS. The carcinogenic potential of MS has been well-documented in man and in experimental animals." While it is best to study ETS directly if possible, ETS differs from MS and SS quantitatively, but not qualitatively. The same chemicals (including carcinogens) are present in MS, SS, ADSS, and ETS but at different relative concentrations and at different absolute concentrations.

## Cancers Other Than Lung

**Michael Johnson, Tobacco Control Section, California Department of Health Services**
1. Comment: Draft presents strong evidence for the increased risk of nasal sinus cancers.

Response: Comment noted.

2. Comment: The draft presents a thorough review, is well done, and takes into account the quality and deficiencies of each study in the evaluation of the findings.

Response: Comment noted.

3. Comment: The section summaries were very useful and provided a good synthesis of the information. The commenter recommends that summaries be written for all sections.

Response: Summaries have now been included at the end of the sections which contain discussions of multiple studies.

4. Comment: The chapter accurately states that the evidence is conflicting and limited for many areas regarding ETS exposure and other cancers.

Response: Comment noted.

**Maurice LeVois, for the Tobacco Institute**
1. Comment: There are too few studies to conclude that there is a relationship between ETS and nasal sinus cancer. With only 28 cases for analysis, the slight risk elevations in nasal sinus cancer reported by Hirayama are based on too few cases to properly account for competing risk factors, even if the required data were available. It is not clear why only the age and occupation of the husband were accounted for in the analysis.

Response: The Hirayama *et al*. (1983) study showed a dose-dependent increase in relative risk from passive smoking with relative risks of 1.7, 2.0, and 2.6 in women whose husbands smoked 1-14, 15-19, or 20+ cigarettes per day, respectively. The 28 deaths in the cohort studied represents an increase in nasal sinus cancer mortality compared with wives of nonsmoking husbands, as illustrated by the relative risks in the study. Age and occupation of the husband were accounted for as potential confounding variables. The commenter does not indicate which other specific risk factors for this type of cancer should have been taken into account.

2. Comment: The results are inconsistent, mostly not significant, and the reported elevations in risk are implausible, since they are higher than risks for active smoking.

Response: The results of the cohort and case-control studies are consistently positive for this rare tumor type in three studies in males and females with different ethnic and cultural backgrounds. The risk for nasal sinus cancers is very low in the general population (about 0.2% of all invasive cancers). The elevations in risk in this study are not higher than those reported for

active smoking. As indicated in Section 7.3.1.1, some studies have indicated up to a 5-fold increase in risk associated with heavy smoking.

3. Comment: Problems with the studies include: they all use a proxy for ETS exposure (spousal smoking), which introduces bias and confounding. Groups with differing socioeconomic level and exposures to relevant risk factors are compared; this also introduces confounding. Hirayama's own data indicate that 10% of the cohort was lost to follow-up. Japanese national mortality statistics show that mortality in those lost to follow-up was more than twice as high as among those not lost. Such a mortality differential could lead to biases of unknown direction and magnitude. Elsewhere, Hirayama published an analysis based more appropriately on wife's age on entry which yielded different results. Hirayama should have analyzed the data using deaths and person-years in attained age categories, as such an analysis might throw light on the inconsistencies seen in Hirayama's results.

Response: The use of the spousal smoking as a dose-surrogate is one method to qualitatively group ETS exposure. The biases and confounding variables introduced by grouping different socioeconomic levels is somewhat accounted for in the study by the adjustment for husband's occupation and age. The loss of 10% of the cohort does not necessarily bias the data toward significance. The uncertainties in the Hirayama data are somewhat balanced by the large sample group examined, the observed dose-response relationship, and the consistency of results with those of the other studies discussed.

4. Comment: No properly designed studies of ETS and nasal sinus cancer have been conducted. The study by Fukuda and Shibata (1990) reports that nasal sinus cancer in women is as strongly associated with ETS exposure as with active smoking, wood working, nasal trauma, and sinusitis or polyps. These other risk factors also resulted in associations in women that were about one third as strong as in males. These results do not make sense. There is no plausible biological basis for equivalent risks associated with such vastly different levels of exposure. Failure to adequately assess confounding by socioeconomic status in this study undermines confidence in the interpretation of the reported smoking-related associations.

Response: The cohort and case-control studies were adequately conducted. The studies contain uncertainties typical of many epidemiological studies, yet yield consistent results, and all show a dose-response relationship of increasing ETS exposure and elevated cancer risk. OEHHA staff agree that additional studies would help clarify further the magnitude of the risk associated wth ETS exposure, as indicated in Section 7.3.1.3. Studies to further characterize the risk by the source of ETS exposure and by timing of the exposure are also needed.

5. Comment: It is premature to conclude that there is suggestive evidence for cervical cancer risk associated with ETS. There are three conflicting studies. Two report positive associations that are implausibly high, given the active smoking risk.

Response: There are now four studies in the revised ETS document; one cohort and three case-control studies. The cohort study and one of the case-control studies did not show statistically significant positive effects on cervical cancer, although positive trends were apparent. The

remaining two case-control studies did show significant positive effects. Therefore, the studies are not "conflicting" as indicated in the comment. Since the toxicokinetics of ETS versus active smoking is not well understood, a direct comparison of the two associations may not be appropriate. There is biological plausibility for the carcinogenic effects on the cervix from exposure to ETS, as discussed in Sections 7.3.2.3 and 7.3.2.4.

6. Comment: The document does not adequately address the importance of the husband's sexual activity as a risk factor for cervical cancer.

Response: Section 7.3.2.2 now includes discussion of the influence of sexual activity as a potential confounder in several studies.

7. Comment: No studies account for the major risk factor for cervical cancer (HPV infection). Since there is a correlation between active smoking and ETS and husband's sexual activity, the ETS/cervical cancer association is more likely a proxy for the husband's sexual activity.

Response: Sexual activity alone does not explain the observed elevations in cervical cancer incidence. For example, in the Coker *et al*. (1992) study, active smoking was a risk factor for cervical cancer irrespective of HPV status (see Section 7.3.2.2).

8. Comment: It is premature to conclude anything about childhood cancers and ETS. There are few studies on this topic, and those that exist provide inconsistent results, as the draft document states. It is worth noting that exposure of a fetus to maternal smoking is not the normal meaning of ETS exposure. Reviews of maternal smoking studies would be more appropriately placed in a separate chapter.

Response: The ETS document states that the evidence whether paternal smoking increases the risk for all childhood cancers, and specifically acute lymphoblastic leukemia and brain tumors, the two leading cancer sites in children, is unclear. The document acknowledges conflicting results and notes the limited number of studies from which to draw conclusions (Section 7.5). The difficulty in separating maternal smoking during pregnancy and transplacental ETS exposure from other sources is acknowledged and discussed in Section 7.5. In short, the document has acknowledged the data gaps and many of the confounding issues raised in the comment.

**Jennifer Jinot of U.S. EPA**

1. Comment: The document provides a nice overview of the ETS literature.

Response: Comment noted.

2. Comment: The commenter suggests several improvements to the document, including minor wording changes, elaboration on the difference between mainstream smoke and ETS, and mention of detection of ETS-related compounds in hair of newborns, as evidence of *in utero* exposure to ETS.

Response: The suggested changes have been incorporated.

**Steven Bayard of U.S. EPA**
Comment: Arguments on biological plausibility for brain tumors based on nitrosamines in ETS are reaching, unless it can be established that these are absorbed by the body and go to the brain in great enough quantities to be suspect. Two problems are 1) that nitrosamines are bladder carcinogens, yet there is no evidence that ETS causes bladder cancer, and 2) one can make the claim that any of the known carcinogens in ETS can cause cancer someplace. I thought the procedure here was to look at ETS as a complex mixture rather than on a compound-by-compound basis.

Response: The role of nitrosamines is discussed in light of experimental findings of neurogenic tumors induced after transplacental exposure to nitrosamines as well as other agents. It is provided as background information in the review. Regarding bladder cancer, determining the role of ETS in its development is difficult because studies to date have been very limited in power to detect effects. The revised draft now contains discussion of the McCredie *et al*. (1994) case-control study, which also describes a positive association between parental smoking and child brain tumors. However, the document still considers the evidence for ETS as a causative agent for brain tumors to be equivocal, as stated in Section 7.4.3.3.

**Clausen Ely and Gio Batta Gori, for the Tobacco Institute**
1. Comment: The draft's main propositions are that environmental tobacco smoke (ETS) exposure increases nasal sinus cancer (NSC) in adults with strong evidence, and cervical cancer with suggestive evidence. Also that parental smoking increases all childhood cancers with suggestive evidence, and that equally suggestive evidence links ETS with acute lymphoblastic leukemia (ALL) and brain tumors in children. By any fair standards, such evaluations do not stand up to scrutiny -- not by the rules of the scientific method, given that none of the studies reviewed is experimental; not by the logically-relaxed "causality criteria" of Bradford Hill which are not met with any visible consistency; and, finally, not by the loosely judgmental "weight of evidence" approach, if and when all weights are noted as reported in the literature and not only those that were arbitrarily selected.

Response: The draft document has attempted to accurately and objectively summarize the findings of each major epidemiological study on ETS. In the cases where the number and magnitude of positive results were not readily explainable by known confounders, the document indicates that there is an effect which warrants further investigation.

2. Comment: ETS levels are thousands of times below mainstream smoke levels. A threshold should be considered for the onset of smoking-related disease, since there exist heavy smokers without disease and because some studies have yielded relative risks below unity. The positive results in ETS studies should be attributed to biases and confounders, given the vast dosimetry differentials compared to active smoking.

Response: (The issue of predicting relative risks from ETS exposure based on those for active smokers: see response to the last comment in the Cardiovascular section below.)

3. Comment: The Hirayama *et al*. and Fukuda and Shibata studies do not adequately account for all important confounding risk factors that should be considered in evaluating nasal sinus cancers. In regard to passive smoking, the Zheng *et al*. study reports an incredible OR = 3.0 (1.0-8.9 95% CI) with no dose trend for nonsmokers exposed to spousal smoking, versus an overall OR=1.2 (0.7-1.9 95%CI) for active smoking. Clearly, this is an indication of massive confounding or reporting bias, making the ETS-related data of this study uninterpretable.

Response: The two studies mentioned above accounted for important confounding variables in the estimation of risk. Fukuda and Shibata (1988, 1990) corrected their calculations based on presence of sinusitis/nasal polyps, nasal trauma, and woodworking. Hirayama *et al*. (1983) adjusted their results based on age and occupation of the husband. The addition of the positive study by Zheng *et al*. (1993) in the revised ETS document further supports the suggestive evidence of the role of ETS in nasal sinus cancer. As stated in the revised ETS document, direct comparisons between smokers and nonsmokers in the Zheng *et al*. study are difficult since the histologic type of nasal sinus cancer was not available.

4. Comment: The evidence for an association with cervical cancer is contradictory. One study reports the same level of risk for exposure to ETS and active smoking, while another reports a protective effect for heavily ETS-exposed subjects.

Response: The results of the study by Coker *et al*. (1992) were not statistically significant and this is stated in the document. A number of important differences exist between the two studies. The "protective effect" in the Coker *et al*. study, mentioned by the commenter, was neither statistically significant, nor dose-related. The study by Sandler *et al*. (1985) is now added in the revised ETS document, and this study also shows a statistically significant elevation in cervical cancer associated with passive smoking, after accounting for a number of confounding variables.

5. Comment: The determination of nicotine/cotinine measurements in cervical mucus is fraught with numerous problems. There is a possibility for sampling contamination. In addition, neither substance is mutagenic or carcinogenic.

Response: The hypothetical possibility of sample contamination when determining nicotine/cotinine concentrations in cervical mucus is a claim that lacks substantiation. The presence of these compounds indicates the biological plausibility of tobacco smoke constituents occurring at the target site of concern. The relative lack of mutagenicity of the two compounds is not relevant.

6. Comment: The association between active smoking and cervical cancer is not clear, and the ETS studies are uncontrolled for confounding and bias.

Response: Section 7.3.2.1 discusses the studies relating to active smoking and cervical cancer. Many of these positive studies account for major confounding variables such as sexual activity variables and infection with HPV.

7. Comment: In the analysis of the risk of ETS and childhood cancers, studies of maternal smoking should not be included here. None of the studies on exposure mentioned by the draft (p.6) is capable of qualifying the draft's statement that "children may have considerable" exposure to ETS.

Response: Various sources of pre- and postnatal exposure to ETS are discussed in Section 7.1.2. Several studies indicate that mother's smoking during pregnancy represents not only tranplacental exposure to tobacco smoke constituents, but also can be used as a proxy variable for postnatal ETS exposure of the child.

8. Comment: There are no data on the levels of ETS that children are exposed to.

Response: It is well known that the quantification of the levels of ETS that children or any other subgroup are exposed to is very difficult. The absence of specific quantitative exposure information does not invalidate the association of the effect with the exposure surrogate.

9. Comment: Since Table 3 shows the risk for childhood cancer associated with ETS to be highest at 0-2 years, and that this risk is reversed by age 5-7, then this childhood cancer in the 0-2 age group is not likely due to ETS.

Response: It remains unestablished that the cause of increased cancer risk in the age range of 0-2 years is due to causes other than ETS exposure.

10. Comment: The report's conclusion that there is suggestive evidence of an increased risk for brain tumors is not supported by the available conflicting data. With good reason, the draft concludes that studies do not support an effect of mothers smoking during or prior to pregnancy. This suggestion has been negated by two recent studies not reviewed in the draft. The studies by McCredie *et al*. (1994) suggest that mother smoking may strongly protect against brain cancer risk, although it provides and additional -- albeit baffling -- suggestion of an association with father's smoking.

Response: The studies by McCredie *et al*. (1994) do not show a "strong protective effect" of mother smoking on brain cancer in children. It is unclear why this statement is being made. The effect of ETS from father's smoking, which was significantly higher than unity, is presented in the document. The McCredie *et al*. studies are summarized and include discussion of confounding factors in Section 7.4.3.2.

11. Comment: Two studies indicate that active smoking reduces the risk of lymphatic leukemia; in others, smoking less than 20 cigarettes/day increases the risk while smoking more than 20 cigarettes/day decreases risk.

Response: The revised document states many of the concerns raised by the commenter in Section 7.4.4.1. As stated in the document, the association with smoking is most consistent for myeloid leukemias, particularly acute myeloid leukemia, and is less consistent for chronic lymphocytic leukemia.

13. Comment: Executive Summary states that there is suggestive evidence of ETS and leukemia risk, which is inconsistent with the text, which states that one can't make a conclusion.

Response: Some data suggest a positive association, but the data are conflicting, as stated in the revised document in Section 7.1.2.4. The Executive Summary and the text are now consistent on this issue.

**Maxwell Layard, for the Tobacco Institute**

1. Comment: The document should clarify the difference between maternal smoking during pregnancy and exposure to ETS.

Response: The revised document discusses the various sources of pre- and postnatal exposure to ETS in Section 7.1.2. Several studies indicate that mother's smoking during pregnancy represents not only tranplacental exposure to tobacco smoke constituents, but also can be used as a proxy variable for postnatal ETS exposure of the child.

2. Comment: There is an inconsistency between the Executive Summary and the text in the conclusions regarding maternal smoking during pregnancy, ETS exposure, and risk of childhood cancer (suggestive vs. inadequate).

Response: The data indicate some suggestions of a positive association, but the data are conflicting, as stated in the revised document in Section 7.1.2.4.

3. Comment: Data do not justify the claim of strong evidence for an association between ETS and nasal sinus cancer or for suggestive evidence for an association between ETS and cervical cancer. The Hirayama *et al*. (1983) study contains many flaws including lack of accounting for potential confounders, such as diet, alcohol consumption, and occupational exposures. In addition, the categorization of subjects is based on husband's age, not wife's age. A logistic regression of these data yield elevations in risk that are non-significant. Since so many cancers were examined in the study, there is an inherent multiple comparisons problem that should be addressed in the document.

Response: The Hirayama *et al*. (1983) study accounted for some potentially confounding variables and did not account for others. Though the study contains flaws not uncommon in epidemiology studies the overall strength of the study is derived from the large sample population. The logistic regression analysis presented, though interesting, appears to increase variability in the estimate of relative risk.

Though many cancers were examined in the study, the overall cancer risk for all cancers was significant, thus reducing concern for artificial multiple comparison chance of detecting a significant effect. The major contributors to this elevation were cancers of the lung, nasal sinus, and brain.

4. Comment: It is biologically implausible that there is a negative association between nasal cancer mortality and active smoking and a positive association with ETS.

Response: The data do not support the commenter's statement that there exists a negative association between active smoking and nasal sinus cancer.

5. Comment: Chance, bias, and confounding cannot be ruled out in the three studies of ETS and nasal cancer risk. They are not all statistically significant, or wholly consistent, and are based on small numbers, and report implausibly higher risks from ETS than from active smoking. They have not adequately controlled for alcohol, diet, or occupational exposures. Also, information on the histology of the cancers in never-smokers is missing in these studies.

Response: All three of the studies show significant elevations in nasal sinus cancer risk from ETS exposure as discussed in the revised document Sections 7.3.1.2 and 7.3.1.3. A number of possible confounding variables were accounted for in the studies.

6. Comment: It cannot be concluded that there is suggestive evidence for an association between ETS and cervical cancer because of the uncertainty regarding active smoking and cervical cancer, and because the studies on ETS and cervical cancer have not controlled for the confounding variable of sexual activity. There may be a correlation between ETS exposure and sexual activity in women. Another potential source of confounding is the sexual activity of the woman's sex partners.

Response: There are now four studies in the revised ETS document; one cohort and three case-control studies. The cohort study and one of the case-control studies did not show statistically significant positive effects on cervical cancer, although positive trends were apparent. The remaining two case-control studies did show significant positive effects. Therefore, the studies are not "conflicting" as indicated in the comment. Since the toxicokinetics of ETS versus active smoking is not well understood, a direct comparison of the two associations may not be appropriate. There is ample biological plausibility for the carcinogenic effects on the cervix from exposure to ETS, as discussed in Sections 7.3.2.3 and 7.3.2.4. Sexual activity alone does not explain the observed elevations in cervical cancer incidence. For example, in the Coker *et al*. (1992) study, active smoking was a risk factor for cervical cancer irrespective of HPV status (see Section 7.3.2.2).

7. Comment: A follow-up to the study by Hirayama of 16 years vs. the 14 year follow-up cited in the document, reaches the opposite conclusion that there is no significant association between cervical cancer and ETS.

Response: The positive associations between passive smoking and cervical cancer in the studies by Hirayama (1981, 1990) are summarized in Section 7.3.2.1. Although sexual activity was not accounted for as a potential confounding variable, the results are consistent in this cohort.

**A. Judson Wells, Kennett Square, PA**
1. Comment: The commenter suggests inclusion of a new study (abstract) on ETS and breast cancer that reports a positive relationship for both active and passive smoking with breast cancer.

Response: The published study by Morabia (1996) has been added to the document.

**Thomas Novotny of U.C. Berkeley**
1. Comment: The document is a well written, thorough review. It is scientifically sound.

Response**:** Comment noted.

2. Comment: The document should mention the difficulties of measuring exposure (*i.e*. biochemical measures, validity of self-report, biases inherent in spousal cohort studies).

Response: These issues are discussed in Chapter 2.

3. Comment: Check that references are all accounted for. Specifically, Brown (1989) article on leukemia should be added to the reference section.

Response: All references have now been checked.

4. Comment: The commenter suggests mentioning other environmental hazards that are regulated, in order to provide a sense of comparative risks.

Response: The purpose of the document is to identify hazards associated with ETS exposure, not to quantify those hazards or to provide comparisons with other hazards.

**Kathy Diehl of U.S. EPA**
The commenter asks whether conclusions can be drawn on maternal smoking and risk for acute lymphoblastic leukemia (ALL).

Response: The document discusses the relationship of childhood leukemia and maternal smoking in Section 7.4.4.3. The overall conclusion is that an association cannot be reached with the current data for reasons summarized in Section 7.4.4.4.

**Michael Siegel**
Comment: The possible roles of chance, bias, and confounding are well-considered in applying a weight of evidence approach.

Response: Comment noted.

## CARDIOVASCULAR EFFECTS

**Betty Jung, Guilford, CT**
Comment: More of the data should be presented in tables, including one or two tables summarizing the results from groups of studies (case-control and cohort) studies. Some description of the benefits of different types of studies would be useful for the reader who does not have knowledge of ETS or epidemiological methods.

Response: Tables are included in the current draft that summarize the effects of ETS on cardiovascular effects in both cohort and case-control studies.

**Jennifer Jinot of U.S. EPA**
Comment: The mechanistic data from animal studies should be included in the draft document. Several specific epidemiological studies and reviews should be added, if specific sections of the draft are to be updated. The review by Wells (1994) should be mentioned in the draft. The Executive Summary should contain a stronger conclusion that ETS is a risk factor for heart disease in nonsmokers. 'Sudden unexpected death' should be defined. Finally, all references need to be accounted for in the reference section. The commenter goes on to suggests many additional specific improvements, not all listed here.

Response: The revised draft document acknowledges the presence of several pertinent animal studies in Section 8.3.7. The review by Wells (1994) has been added to the revised draft in Section 8.0.2. Section 8.0.3 discusses recent evidence of associations between ETS exposure at home or at work and coronary heart disease (CHD), which relates to the concern by the commenter of the possibility of exposure misclassification of non-smokers tending to lower risk estimates. The discussion of Hole *et al.* (1989) in Section 8.1.1 has been revised to reflect the concern that the unadjusted increase in risk for angina is 2% rather than 11%.

**Joseph Wu, for the Tobacco Institute**
1. Comment: The epidemiological studies do not provide evidence of a causal association. The epidemiological studies do not have consensus on what constitutes a valid biomarker for ETS exposure, and the use of proxy spousal smoking is imprecise in comparison to obtaining direct chemical or physical measures through the use of station or personal monitors. In addition, the assessment of CHD-linked morbidity and mortality may be imprecise because the diagnosis of CHD is imprecise.

Response: The use of spousal smoking as a proxy for ETS exposure, though imperfect, is the only feasible way in which to categorize exposures in most studies. Although the studies do not specify why personal monitors were not used to measure exposure to ETS, one could speculate that the cost of distributing tens of thousands of personal monitors over many years to the subjects would be prohibitive.

Diagnoses of CHD may, on occasion, be imprecise. However, CHD is a very well recognized disease that is very often successfully diagnosed.

2. Comment: The draft must address the multiple risk factors for CHD, especially sex-specific ones.

Response: The presence of multiple risk factors in CHD is acknowledged. The document describes the epidemiology research which shows a positive association between ETS exposure and elevation of CHD. Many of the studies addressed potential confounding variables. All gender-specific effects reported used appropriate gender-matched controls for comparison. Many of the risk factors mentioned by the commenter are not linked to smoking (*e.g.*, diabetes mellitus), therefore they would not be expected to be potential confounding variables between cases and controls.

3. Comment: The mechanisms proposed for the cardiovascular effects of ETS are not biologically plausible. Mechanistic studies are the only way to validate the observations in the epidemiological studies. Several experimental results and epidemiological studies provide alternative interpretations of these data, for example: (a) cigarette smoke has vasodilatory effects (in the pulmonary circulation), as well as vasoconstrictive effects. To emphasize exclusively the vasoconstrictive properties of exposure to cigarette smoke (*e.g.*, ETS) is a bias which is unjustified based on currently available scientific literature; (b) data do not support the hypothesis that ETS exposure results in increased platelet reactivity, positive studies use non-standard platelet aggregation assays; (c) it is unclear whether plasma LDL/HDL levels are modulated by ETS. Contrary to expectation, smoking does not constitute a risk for CHD in Far East countries with a high prevalence of smoking, as the average plasma LDL and the LDL/HDL ratios are relatively low; (d) it is unclear whether ETS/active smoking has an effect on cardiac functions, or whether such effects are biologically relevant (*e.g.*, a mitochondrial function study is discussed in the document).

Response: Experimental studies on ETS are appropriate for investigation into the mechanisms involved in the various health effects observed in the epidemiological studies. More experimental research would help strengthen the epidemiological findings.The vasoconstrictive and other hemodynamic properties of smoking are mentioned in Section 8.3.5. The observation of a short-term dilatory effect of ETS in the bronchial circulation due, possibly, to the presence of nitrogen oxide, is interesting, but does not contradict the findings discussed in the document.

ETS exposure does appear to affect platelet aggregation. The assays used in the studies mentioned measured platelet aggregation and endothelial cell number as a function of exposure to tobacco and other varieties of smoke. The experiments appear to be well-conducted and were peer-reviewed. It is unclear what the commenter means by a “standard” method for measuring such effects. There is uncertainty regarding the mechanism involved in the lowering of HDL by exposure to ETS. The appropriate comparison for incidence of CHD in Far East countries should be between those exposed to tobacco smoke and those not exposed within the population studied, since there are multiple dietary and other factors that influence these parameters.

**Gio B. Gori, for the Tobacco Institute**

1. Comment: One cannot conclude that there is an association between ETS and CHD, based on the following: (a) the concentration of side-stream smoke is so low, compared with mainstream smoke associated with active smoking, that the dose will be very small; (b) the data for active smoking (human biomarkers data: urine mutagenicity, SCEs in peripheral blood, DNA adducts in oral tissues and lung cancer tissues, sperm mutations) support a threshold of less than 10 cigarettes/day, or a NOAEL for CHD of 4-5 cigarettes/day, thus ETS cannot be a risk factor, (c) the epidemiological studies reviewed in the draft are of limited sample size and statistical power. A figure supplied by the commenter vividly shows that the instability of results is more pronounced in studies of small sample size. The studies derived from the databases of the American Cancer Society and of the National Center for Health Statistics have massive power and are decisive in concluding that the claim of an association between ETS exposure and CHD risk cannot be sustained scientifically.

Response: The toxicokinetic differences between mainstream and sidestream smoke have not been precisely defined. Therefore, it may not be appropriate to compare active and passive smoking directly. Nevertheless, several studies described in Sections 8.1 and 8.2 of the document show that light smoking (*e.g.*, less than 10 cigarettes/day) still results in significant elevations in risk of CHD. Each study described in the document was selected based on its completeness and ability to yield decisive information. Strengths as well as limitations of each study are discussed in the document (*e.g.* Section 8.1.1). Some studies, such as the cohort study by LeVois and Layard (1995) contained considerable limitations such as reporting inconsistencies and unclear subject selection processes, but were included since they may still yield some useful information.

A complete discussion of all 17 studies of the effects of ETS on CHD, including the three that do not show an association, is included in the document. The document acknowledges that two of the three studies were negative, and points out that, despite their large power level, serious methodological flaws in those studies may have influenced the result toward the null.

2. Comment: The draft selectively sites clinical and laboratory studies that support mechanistic hypotheses, without identifying the shortcomings of these studies or citing other studies which do not support the hypotheses.

Response: OEHHA staff have endeavored to present a factual and unbiased summary and analysis of the data on ETS and CHD. As described above, several negative studies are discussed in the ETS document. Where experimental studies yielded mixed results, these have been reported in the description of each study. In addition, when serious flaws existed in the studies, these are discussed in the document.

3. Comment: Animal studies are not relevant to ETS in humans; animals are exposed to ETS under different conditions than humans are and differences between animals and humans make comparisons unrealistic.

Response: The ETS document focuses primarily on human studies. Section 8.3.7 briefly discusses animal studies. The animal studies are discussed to illustrate that the atherosclerotic process from short-term exposure to ETS also occurs in other species.

4. Comment: The hypothesis of ETS and increased blood clotting capacity is not supported by the data. A study on the Kuopio cohort in Finland by Wilson *et al*. (1993) did not find a correlation between plasma fibrinogen levels and smoking.

Response: Section 8.3.5 describes several studies that show that platelet activation, platelet sensitivity to prostaglandins, and endothelial damage occurs after brief exposure to ETS. In addition, Section 8.3.6 describes numerous studies that show a positive association between active smoking and elevated fibrinogen levels. At present, only a single study contains data on ETS and fibrinogen levels, which gave mixed results, as discussed in the document.

5. Comment: There is no evidence that ETS raises cholesterol levels, raises blood pressure, reduces respiratory function, or increases CO levels high enough to aggravate angina. Many studies show that there is no correlation between active smoking and cholesterol. The Framingham Offspring Study and a Kaiser Permanente study report that cigarette smoking was not correlated with lipoprotein (a) levels. A Japanese study also found no difference in plasma cholesterol between smokers and nonsmokers. The massive WHO-MONICA study actually showed a strong negative association between regular smoking and high cholesterol in male populations.

Response: As discussed in Section 8.3.4, in addition to numerous reports of altered cholesterol levels by active smoking, the only two studies specifically involving ETS do show a significant elevation in the total cholesterol/HDL ratio, which is a clinical benchmark for CHD risk. The effects of ETS on respiratory function is not specifically addressed in the cardiovascular chapter. The increases in COHb levels as a result of ETS exposure are discussed as contributing factors to the overall elevated risk of CHD, not as the sole contributing factor.

**A. Judson Wells, Kennett Square, PA**

1. Comment: Some recently published studies (given by the commenter) should be added to the review.

Response: The references given by the commenter have been added where new original data were presented.

2. Comment: The description of the Hole *et al*. (1989) study says that nonsmokers included exsmokers, whereas the nonsmokers were actually never smokers.

Response: The inconsistency in the description of the Hole *et al.* (1989) study has been corrected. The subjects and controls were, in fact, never-smokers.

3. Comment: The discussion of the Butler thesis should state that RR was only adjusted for age. The He (1989) paper should be added and the Butler thesis should be deleted in order to correct the list of studies that adjusted for other heart risk factors.

Response: The document has been changed to reflect the conclusions reached in the Butler thesis.

4. Comment: There are some inconsistent cholesterol values on pages 28 and 29 [of the previous draft] in the discussion of the He (1989) paper.

Response: The values mentioned by the commenter have been corrected in the document.

5. Comment: The data from Dobson *et al*. (1991a) are internally inconsistent and could be deleted from the document.

Response: Due to the limited number of studies on the subject, the Dobson *et al*. (1991a) study was included, despite the mixed results indicated.

6. Comment: The animal data are very important for providing mechanistic information.

Response: Section 8.3.7 on animal evidence has been expanded.

7. Comment: The lipid profile data in children are strengthened by a new study by White *et al.* (1992).

Response: With a few exceptions, findings presented in meeting abstracts have not been included.

8. Comment: The overall comparison of fatal vs. non-fatal CHD risk does not show that fatal CHD outcomes have a higher risk than non-fatal outcomes, as discussed in the document.

Response: Several of the studies discussed in Sections 8.1 and 8.2 indicate that risks for fatal outcomes are higher than for non-fatal outcomes.

**Maurice LeVois, for the Tobacco Institute**

1. Comment: Discussion of possible biological mechanism of action is largely speculative, based on minimal preliminary data (1-2 studies). It is not clear whether these changes are related to ETS, since they are reported for extremely low levels of ETS exposure and they do not demonstrate a dose-response effect. We do not know if these changes have any adverse clinical effect.

Response: There is uncertainty about the mechanisms involved in elevated CHD from ETS exposure. Several mechanisms have been investigated in clinical studies and animal experiments, as discussed in Section 8.3 of the revised document. Various interrelated processes are discussed with relation to their contributions to the clinical manifestations of myocardial

infarction, including: atherosclerosis, thrombosis, coronary artery spasm, cardiac arrhythmia, and reduced capacity of blood to deliver oxygen. Active smoking appears to influence all of these mechanisms. The evidence of effects of ETS on internal and common carotid wall thickness, endothelial function, exercise tolerance, lipid profile, platelet function, and fibrinogen levels is consistent with the hypothesis that ETS exposure increases risk of CHD.

2. Comment: The discussion of the epidemiological studies is accurate and useful. The document should emphasize that the studies are small, and that bias and confounding cannot be ruled out, making interpretation of the relative risks uncertain. It is impossible for small studies to properly adjust for potential confounders. The draft concludes that there is an association between ETS and CHD, but this is a very weak association (1.3). Relative risks of less than 2 are difficult to interpret, and it is hard to distinguish between bias and confounding and real effects.

Response: There are 14 studies that show increases in relative risk for CHD from exposure to ETS. In addition, five quantitative reviews, including four meta-analyses indicate significant risks of CHD from ETS exposure. The collective evidence supports an increased relative risk of 30%. Regarding confounding factors, the estimates of risk were almost always strengthened by adjustment for other cofactors.

3. Comment: A meta-analysis of the spousal smoking studies is of little use, since it cannot correct for common study design weaknesses, and because of publication bias. A meta-analysis will simply exaggerate the significance of these problems.

Response: In evaluating the body of evidence to reach conclusions regarding the relationship between cardiovascular effects and ETS exposure, weaknesses of individual studies were taken into account.

4. Comment: There are only three studies on workplace exposure to ETS; the data are not sufficient to conclude that workplace exposure increases risk of CHD.

Response: The revised document seems to address the commenter's concern. Regarding the five workplace ETS studies now reviewed, the revised document (Section 8.2) states that most of the studies "...had limited ability to investigate the role of workplace ETS exposure since only small numbers of subjects had jobs outside the home."

5. Comment: Publication bias could account for the number of positive vs. negative studies. The attached (unpublished) manuscript that analyzes data from two large American Cancer Society studies finds no association between ETS and CHD, and concludes that the highest risks are found in the smallest studies. The small size of most of the ETS/CHD studies is a major design flaw.

Response: A complete discussion of the 17 studies of the effects of ETS on CHD, including those that do not show an association, is included in Sections 8.1 and 8.2. Analyses of the American Cancer Society studies are discussed at length, including the analysis authored by the

commenter. The discussion in the current version of the document has been expanded and further addresses issues raised by the commenter.

6. Comment: The positive studies have not adequately controlled for confounding. The studies are too small, have poor designs, and use spousal smoking as the definition of ETS exposure which increases the likelihood of confounding, since there is spousal concordance on numerous CHD risk factors (exercise, diet). Studies do not address the different pattern of CHD in females and males, which is important since the majority of study subjects are female. The document should take into account menopausal status and hormone-replacement therapy use. The Framingham study addresses many confounding risk factors, has large statistical power, and has nearly 100% follow up. No other ETS/CHD epidemiology study approaches this in terms of research quality.

Response: The stratification of study groups by age category partially addresses the concern raised regarding hormonal status and menopause. Further study of the impacts of hormone replacement therapy in smokers and ETS exposed would be of interest, as the commenter suggests. The Framingham study results are discussed in Section 8.2 of the revised document. The study has been criticized for including a small percentage of women smokers, and because most women examined were light smokers.Thus, despite the large sample size, the actual power of the study was limited.

7. Comment: The relative risk of active smoking is less than the figure of 2.5 noted in the document for comparisons with risks of ETS exposure. If one assumes that ETS exposure 100 times less than active smoking exposure, then the 30% excess risk for CHD associated with ETS is 10 times higher than expected.

Response: There are a number of quantitative issues to consider in predicting the relative risk of ETS exposure from that of active smoking. These include: the identity and magnitude of the exposure of the critical constituents of smoke causing the effect, the dose-response relationship for these constituents, the degree of exposure to ETS among active smokers, the baselines for the relative risk estimates in the two groups, and tobacco smoke exposures among those presumed to be unexposed. These considerations appear to have been taken into account only to a limited degree by the commenter.

## EXPOSURE MEASUREMENTS AND PREVALENCE

For ease of reference, the response to public comments received are grouped by the sections in the chapter.

**Richard A. Carchman (Philip Morris), Mary E. Ward (R. J. Reynold), and Larry C. Holcomb (for the Tobacco Institute)**

Comment: The inference of physical and chemical properties of ETS from those of exhaled mainstream smoke (exhaled MS) and sidestream smoke (SS) was questioned. The comments noted that the chemical composition and physical properties (*e.g.,* particle size distribution) of exhaled MS and SS change as they age and mix with room air. As a result, they believe the chemical composition of ETS is quite different from that of exhaled MS or SS. Commenters suggested that because of dilution and aging, the chemical composition and physical properties of ETS are different from those of a mixture of SS and exhaled MS.

Response: SS, exhaled MS, and the products of the dilution and aging of the two all contribute to ETS. Given the many reactive chemicals identified in ETS, certain changes in the chemical composition and physical properties of ETS take place as it ages and moves away from the source. Chemical composition of MS and SS are similar as they are both produced by the combustion of tobacco and paper. As described in the chapter, approximately 400 compounds have been detected in both SS and MS. However, due to differences in the temperature of combustion of the tobacco, pH, and degree of dilution with air, emission rates of some of the constituent chemicals such as N-nitrosodimethylamine, 4-aminobiphenyl, and pyridines are known to be significantly higher in SS than in MS.

Dilution by itself does not affect the chemical composition of a mixture, it only decreases the constituent concentrations. As discussed in the chapter, aging of ETS is a complex process that includes interaction of reactive chemicals, condensation of constituent chemicals onto suspended particles, change in particle size distribution, and removal of some of the suspended particles by a number of physical forces. Some ETS constituents such as DDT, polyaromatic hydrocarbons and heavy metals are not reactive and are not likely to be chemically altered through the aging process.

Section 2.3.2 acknowledges the high spatial and temporal variation of ETS concentrations and discusses some of the contributing factors such as rate of tobacco consumption, room size, ventilation rate, and proximity of the sampling device to the smoker. Section 2.3.3 cites some studies which reported that concentrations of nicotine in air due to ETS ranged about 100-fold, from 0.3 to 30 $\mu g/m^3$. Under some extreme conditions, nicotine levels as high as 1,000 $\mu g/m^3$ have been reported.

**Richard A. Carchman (Philip Morris), Mary E. Ward (R. J. Reynolds), Stanley Greenfield (ICF Kaiser)**

Comment: The validity of predicting the toxicity of a complex mixture such as ETS based on the toxicological information of its constituents was questioned.

Response: The chapter provides background information on exposure and does not reach conclusions regarding the overall toxicity of ETS. The conclusions of the chapters on health effects are primarily based on epidemiological evidence for ETS exposure and the effect in question. Nonetheless, the scientific practice of using toxicological information on constituents of a complex mixture to evaluate the overall toxicity of the mixture has been widely applied to petroleum products, mixtures of polyaromatic hydrocarbons, and mixtures of dioxin-like compounds.

Comment: The relevance of the carcinogenicity information presented in Chapter 2, most of which was obtained from studies in animals exposed to carcinogens through means other than inhalation, was questioned.

Response: Chapter 2 lists carcinogens in tobacco smoke (Table 2.2), some of which were identified as carcinogens through studies in animals using exposure pathways other than inhalation, the primary route for ETS exposure. There is no compelling scientific evidence to indicate that the organic and inorganic chemicals listed in Table 2.2 would not be carcinogenic by the inhalation route.

Comment: The section "Biologically Active Constituents of ETS" did not include dose-response information in the discussion, and did not put ETS constituent levels in context by giving existing occupational exposure standards, or total exposure to these substances.

Response: The purpose of the section on biologically active constituents (Section 2.2.2) is to identify and discuss some of the toxicological properties observed for ETS constituents as background for chapters which evaluate the health effects of the ETS as a whole. The text discussing the effect of ETS constituents on mucociliary function has been modified to indicate that the adverse effect would occur only at sufficiently high concentrations.

**Mary E. Ward (R.J. Reynolds)**

Comment: In many places of Section 2.3, the term "exposure" was used to refer to concentration levels without reference to duration, or to potential durations without reference to concentration levels.

Response: The introduction to this section has been revised to emphasize that the purpose of assessing ETS exposure in most of the reviewed epidemiological studies was to classify the subjects into exposure categories (*e.g.*, low, high) . We agree that due to the high spatial and temporal variation of ETS constituents, it is very difficult to accurately measure the long-term ETS exposure of an individual. Nevertheless, many techniques discussed in this chapter have proven to be useful for the purpose described above.

**Larry C. Holcomb (for the Tobacco Institute), Mary E. Ward (R. J. Reynolds)**
Comment: The use of nicotine, respirable suspended particulates (RSP), volatile organic compounds (VOCs), and polyaromatic hydrocarbons (PAHs) as markers of ETS was criticized. Studies were cited showing that nicotine levels in air often do not correlate well with other constituents of ETS. According to the commenters, ETS is not the only or even a major source of RSP, VOCs, and PAHs, and the use of these chemicals as markers of ETS is problematic.

Response: The document acknowledges that measured levels of nicotine, RSP, VOCs, and PAHs may not correlate perfectly with all the constituents of ETS. However, such measurements are still useful. For example, airborne nicotine is unique to tobacco smoke and provides information on other volatile and semi-volatile constituents of ETS in air; RSP measurements provide some information on the level of less volatile chemicals associated with suspended particulates; some VOCs and PAHs are not only markers of ETS, but because of their toxicological properties, they are also contaminants of interest in many studies. We agree that because RSP, VOCs, and PAHs are not specific to ETS, care must be taken in reviewing studies which use their concentration levels as indicators of the degree of ETS exposure.

**Larry C. Holcomb (for the Tobacco Institute), Richard A. Carchman (Philip Morris)**
Comment: The statement that residential and nonresidential nicotine exposure are comparable is not supported by recently published personal monitoring data. Average nicotine and RSP concentrations measured in homes or workplaces are lower than those reported in the chapter.

Response: The chapter states that based on the data collected from the mid-1970s through 1991, concentrations of nicotine in the workplace were found to be similar to those measured in residences. Because of the recent increase in smoking restrictions in the workplace, it is reasonable that more recent studies may find higher levels of ETS at home than in the workplace. However, many of the nicotine and RSP levels mentioned by one of the commenters are well within the range of concentrations of nicotine (0.3 to 30 $\mu g/m^3$) and RSP (5 to 500 $\mu g/m^3$) cited in the chapter.

**Mary E. Ward (R. J. Reynolds)**
Comment: The validity of the statement "The most significant location of exposure for adult nonsmokers was the workplace, although other locations …were also important (pp 53)" was questioned, and several recent studies showing that exposure to ETS at home is more significant than that at work were cited.

Response: The statement "the most significant location of exposure for adult nonsmokers was the workplace, . . ." was based on a number of studies conducted in the late 1980s in California. The next paragraph discusses the increasing restrictions on smoking in the workplace and public locations which would lead to a decrease of exposure to ETS at work. This statement is not in conflict with some of the recent surveys conducted between 1994 and 1995 which indicate that ETS exposure at home could be more important than that at work.

**Richard A. Carchman (Philip Morris)**
Comment: A "cigarette equivalent" approach should be used to compare the amount of nicotine and RSP in ETS with that in MS. Studies were cited which reported that using this approach, exposure to nicotine from ETS is about 100 to 1000 times lower than from MS.

Response: Presumption of quantitative relationships between constituents in MS and ETS can be problematic. The ratio of constituents in MS and ETS differs; in addition constituents differ in their pharmacokinetic properties as well as in their dose-effect relationships.

**Mary Ward (R. J. Reynolds)**
Comment: There is an inconsistency in the chapter. Though it is stated in Section 2.3.1 that "Modeling exposure on the basis of measured or modeled air concentrations and the time an individual spends in a specific environment, another indirect method, is not discussed in this document", results obtained from mathematical models were referenced (Table 3-5 of the U.S. EPA document) on Page 11 [of the previous draft].

Response: While Chapter 2 may present results of models, the modeling method used to obtain the results is not discussed.

**Larry Holcomb (for the Tobacco Institute), Mary E. Ward (R. J. Reynolds), Richard A. Carchman (Philip Morris )**
Comment: Biologic cotinine is not specific to ETS and cannot be used as a biomarker indicating ETS exposure. Cotinine levels measured in saliva, serum, and urine correlate poorly with levels of constituents of ETS in air. Regarding usefulness of using cotinine to validate self-reports of ETS exposure, a number of studies did not detect cotinine in individuals who recalled exposure to ETS.

Response: The limitations in the use of cotinine as a marker of ETS exposure are discussed. As stated in the chapter, low levels of nicotine are found in some foods, for example, in eggplants, green peppers, and tomatoes, but at relatively low levels. The efficiency of nicotine absorption through eating is believed to be much lower than through inhalation. Dietary sources of nicotine do not contribute significantly (less than 2%) to the measured serum cotinine levels (Pirkle *et al.*,1996). Concentration of cotinine in saliva, serum, and urine are used by many researchers to estimate the level of exposure to ETS. In a number of studies, epidemiologists use this technique to validate self-reports of smoking status and ETS exposure. This method was not used to and does not claim to be able to accurately quantify exposure to the many constituents of ETS. As discussed in the chapter, measurement of cotinine levels in physiological fluids is most useful in identifying active smokers among self-reported nonsmokers.

**Richard Carchman (Philip Morris)**
Comment: Noting that Friedman *et al.* showed over 47% of women married to smokers reported zero hours of exposure at home, the commenter suggested that "using the spouse's smoking status to classify persons resulted . . . . in a considerable amount of misclassification."

Response The data collected by Friedman *et al.* showed there was a strong correlation between duration of passive smoking and spouses' smoking habits.

**Richard Carchman (Philip Morris)**
Comment: The use of questionnaires to estimate ETS exposure was criticized because this approach cannot provide information on the concentration or frequency of ETS exposure.

Response: The report notes that studies on the reliability of questionnaire responses indicate that qualitative information obtained is generally reliable, but that quantitative information may not be.

**Mary Ward (R. J. Reynolds), Richard Carchman (Philip Morris)**
Comment: Based on the study published by Pron *et al*. that examined the reliability of self-reported ETS exposure histories, commenters suggested that consistency of responses about exposure between the initial and re-interview was poor, and correlations between responses were low, especially for questions related to intensity and duration of exposure.

Response: In the cited paper, Pron *et al*. described a study designed to examine the reliability of passive smoking histories reported in personal interviews. A total of 117 control subjects initially interviewed in a lung cancer case-control study were re-interviewed on average six months later. Responses obtained from the two interviews were compared to examine the reliability of ETS exposure information. Pron *et al.* found that "The reliability of reported exposure to spouse's smoke was high for both sexes. Exposure to maternal smoke was more reliably reported than exposures to smoke of the father, siblings, children, and other relatives." Pron *et al.* did find the duration of exposures to ETS were less reliably reported, and suggested that when improvements in reliability are impossible, increasing sample size is an alternate strategy to deal with the effects of random error associated with exposure status on risk estimates.

Comment: Smoking information provided by surrogate respondents is not reliable as demonstrated in a number of studies (Lerchen and Samet, 1986; Kolonel *et al*., 1977; Sandler and Shore, 1986; and Brownson *et al.*,1992). The work of Brownson *et al.* on the reliability of questionnaires showed responses of cases were less reliable than those of controls and suggested that this may bias the relative risk estimates on the high side.

Response: Authors of the studies cited found surrogate respondents were able to provide reliable information regarding the smoking status of the subject. Quantitative information, such as number of cigarettes consumed per day, provided by surrogates was found to be useful but not as accurate. These findings are discussed in Section 2.5.1. Brownson *et al.* observed a slightly higher reliability of information on smoking provided by controls than by cases, but results were based on relatively few case re-interviews (n=37). The authors suggested that the case re-interviews may be biased towards lower agreement due to the effect of the illness among living cases or due to proxy information.

**Richard Carchman (Philip Morris)**

Comment: Self-reported exposures to ETS do not correlate well with levels of nicotine and RSP measured.

Response: Limitations of ETS exposure information derived from self-reported exposures (questionnaires) are discussed in Section 2.5. It is acknowledged that questionnaires, widely used in assessing ETS exposure, provide accurate qualitative information on self-reported exposure to spousal, parental or other household smoking, although quantitative information is less reliable.

**Richard Carchman (Philip Morris)**
Comment: The tremendous publicity generated by the U.S. EPA's classification of ETS as a "known human" carcinogen might have biased the recall of nonsmoking lung cancer cases.

Response: U.S. EPA classified ETS as a known human carcinogen in 1992. Most of the data collection for studies cited occurred before that time.