Comments of Maurice E. LeVois, Ph.D, (on behalf of Lorillard Tobacco Company).

Comment 1:

These comments are submitted at the request of the Lorillard Tobacco Company in response to the California Air Resources Board (ARB) and Office of Environmental Health Hazard Assessment (OEHHA) Draft Report Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003. The comments focus on the use of epidemiological data on environmental tobacco smoke (ETS) as the basis for their conclusions about the risk of sudden infant death syndrome (SIDS), lung cancer, nasal sinus cancer, breast cancer, and heart disease.

I have previously filed detailed comments on draft chapters of the California Environmental Protection Agency's (CA/EPA) 1997 ETS Risk Assessment dealing with lung cancer, cancers other than lung, heart disease, and reproductive effects. Many of my earlier comments were not addressed by CA/EPA, either in the final draft of the 1997 report, or in Appendix A, which purported to address submitted comments. Since the current ARB/OEHHA Draft Report draws extensively on the CA/EPA 1997 ETS Risk Assessment, I will first summarize my comments on that document. I will then comment on the relevant epidemiological studies published after the 1997 ETS risk assessment, and on the ARB/OEHHA methods and conclusions presented in the current Draft Report.

Response:

The earlier document (Cal/EPA, 1997) has been subjected to an extensive process of public comment, review by the Scientific Review Panel for Toxic Air Contaminants, and has been published by the National Cancer Institute as a monograph following their review. The purpose of the current document is to examine more recently published findings which may extend or modify conclusions reached in that document, not to re-open debates which were satisfactorily dealt with in the earlier report. Accordingly, the recently issued call for public comment did not invite comments on the 1997 document, and OEHHA will only respond to those comments which appear to have relevance to the more recent report.

Comment 2:

SECTION I: Summary of comments that apply to both the 1997 and the 2003 reports.

The Draft Report states that: "An effect is judged to be causally associated with ETS exposure when a positive relationship between ETS exposure and the effect has been observed in studies in which chance, bias and confounding could be ruled out with reasonable confidence." This brief definition of causation is vague and subjective. It says nothing about strength of association. Weak spousal smoking associations are below the resolving power of the epidemiological methods employed to study ETS. The definition ignores inconsistent epidemiological findings, including statistically significant negative results, obtained using essentially the same research designs and methods. It ignores inconsistent evidence relating to mechanism and biological plausibility. It is my opinion that none of the reported associations between ETS exposure and health effects described in the Draft Report can rule out bias and confounding with reasonable confidence and, therefore, the ETS epidemiological studies do not meet even the inadequate stated requirements.

Response:

The summary statement quoted is adequately qualified elsewhere in the document. The commentator is apparently concerned with the issue of "strength of association", which is itself a "vague and subjective" concept but has been used in the past to justify the discounting of effects which are statistically significant (e.g. 95% lower confidence bound on odds ratio > 1.0), but less than some arbitrary higher level (e.g. odds ratio > 2.0 or > 3.0). OEHHA, along with many other commentators, has pointed out on a number of occasions that while this may be a useful "reality check" for rare outcomes such as specific occupationally associated cancers, it is inappropriate and unreasonable to apply such criteria for increased risks of common outcomes such as lung cancer or heart disease. Indeed, for several such outcomes the desired "strength of association" criterion could only be met if mortality in the study population from that single cause approached 100%, which is intrinsically improbable. Most of the outcomes studied are common chronic diseases, with multiple risk factors. Many of these established risk factors have only moderate associations with the diseases, but occurring together greatly increase the risk of disease in an individual. Furthermore, the attributable risk due to ETS can be very high, even if the relative risk is only moderate, because of the high prevalence of the diseases and the widespread exposure to ETS.

The comment refers to "statistically significant negative results", but no such results are discussed by OEHHA or brought to our attention by the commentator. There are a number of studies where the confidence bounds on relative risk include 1.0, i.e. the results are consistent with the null hypothesis, but this is not significant negative evidence, merely the absence (in isolation) of statistically significant positive evidence for an association.

Comment 3:

Objective methods and criteria were not used in the CA/EPA 1997 ETS Risk Assessment, nor are they used in the current Draft Report. The authors of the 1997 report, and of the current report as well, say they have used a "weight of evidence" approach, but their definition of what they mean by this is again vague and entirely subjective. No comparison of observations with objective standards is ever described. The Draft Report should follow the U.S. EPA guidelines for evaluating human data as part of carcinogen risk assessment (EPA, 1999). Similar guidelines were in place in 1996, but they were not followed in the 1997 report, nor are the current EPA guidelines being followed in this Draft Report.

In section **2**.2.1.2. *Criteria for Assessing Adequacy of Epidemiologic Studies* the EPA guidelines list ten criteria that should serve as the basis for an objective assessment of each study. Of particular relevance in evaluating the ETS epidemiological studies are criterion (2) proper selection and characterization of the exposed and control groups and (3) adequate characterization of exposure. The spousal smoking definition of ETS exposure is a poor proxy for the exposure of interest and its use introduces systematic socioeconomic and lifestyle differences between exposed and control groups. Of equal relevance are criterion (6) proper consideration of bias and confounding factors and (7) adequate sample size to detect an effect. None of the ETS case-control studies has ruled out active smoker misclassification, and none of the prospective studies has controlled adequately for confounding.

Response:

OEHHA is well aware that the U.S. EPA has published various guidelines and exemplary guidance on epidemiological methodology. Although not in any sense bound by such guidelines, OEHHA is in broad agreement with the principles espoused by U.S. EPA. However, OEHHA does not agree with the commentator's assertion that either report departs significantly from these principles. It is not possible to deduce from the text of the comments, which is non-specific, where exactly the departures from U.S. EPA's recommended practice occur, or what OEHHA could do to resolve the commentator's dissatisfaction.

Comment 4:

The EPA guidelines describe the following criteria that should be used in the Draft Report to evaluate each study:

1. Population Issues

The ideal comparison would be between two populations that differ only in exposure to the agent in question. Because this is seldom the case, it is important to identify sources of bias inherent in a study's design or data collection methods. Bias can arise from several sources, including noncomparability between populations of factors such as general health (McMichael, 1976), diet, lifestyle, or geographic location; differences in the way case and control individuals recall past events; differences in data collection that result in unequal ascertainment of health effects in the populations; and unequal follow-up of individuals. Both acceptance of studies for assessment and judgment of their strengths or weaknesses depend on identifying their sources of bias and the effects on study results. Comment: There is no ETS case-control study that addresses all of these issues. Most ETS studies present no data at all that assess their control or lack of control of any of these issues.

Response:

All epidemiologic studies are subject to the biases listed above. However, nearly all studies included in the report appeared in high quality peer reviewed journals, and evaluation of all sources of bias is part of the review process. Many manuscripts are rejected based on factors that may have introduced too much bias into the studies. The studies selected for this report were deemed to be of high quality. Although no epidemiologic study can completely rule out bias, the consistency of results across many studies is a good indication that the results are due to a true association between the risk factor and the disease.

Comment 5.

2. Exposure Issues

For epidemiologic data to be useful in determining whether there is an association between health effects and exposure to an agent, there must be adequate characterization of exposure information. In general, greater weight should be given to studies with more precise and specific exposure estimates.

Questions to address about exposure are: What can one reliably conclude about the level, duration, route, and frequency of exposure of individuals in one population as compared with another? How sensitive are study results to uncertainties in these parameters?

Comment: Spousal smoking and retrospective questionnaire ratings of workplace exposure are poor proxies for true ETS exposure.

Response:

Exposure assessment is frequently a difficult proposition in epidemiological studies, and this is especially true where past exposure ascertainment relies on inadequate questionnaires. However, questionnaires are the only means of assessing past ETS exposure, and well-designed questionnaires can provide meaningful data. Recent studies have found good agreement between questionnaire responses about ETS exposure and serum cotinine levels. For example, a study of 680 pregnant women in California (DeLorenze et al., 2002) found that self-reported total hours per day of ETS exposure was a significant predictor of log serum cotinine.

Comment 6:

3. Confounding Factors

A confounding variable is a risk factor, independent of the putative agent, that is distributed unequally among the exposed and unexposed populations (e.g., smoking habits, lifestyle). Adjustment for possible confounding factors can occur either in the design of the study (e.g., matching on critical factors) or in the statistical analysis of the results.

Comment: Few ETS studies measure socioeconomic status, let alone all of the other health-related diet and lifestyle differences between smoking and non-smoking study groups.

Response:

Most of the studies measured and controlled for correlates of socioeconomic status such as education, income level, and ability to pay for health care and occupational status. Many measured other lifestyle issues that were deemed appropriate. Studies that did include these measures when appropriate were regarded as higher quality studies in the OEHHA review.

Comment 7:

4. Sensitivity

Sensitivity, or the ability of a study to detect real effects, is a function of several factors. Greater size of the study population(s) (sample size) increases sensitivity, as does greater exposure (levels and duration) of the population members.

A unique feature that can be ascribed to the effects of a particular agent (such as a tumor type that is seen only rarely in the absence of the agent) can increase sensitivity by permitting separation of bias and confounding factors from real effects.

Comment: Most of the ETS studies are small and have very low statistical power. This not only limits their ability to observe a statistically significant association, it also limits their ability to control for bias and confounding. None of the ETS studies involve such "unique features." Instead, all of the ETS studies are attempting to find associations with very common health outcomes.

Response:

Many of the studies were, in fact, very large (including more than 1,000 study subjects) and had sufficient power to detect an effect. Furthermore, more weight was placed on studies with statistically significant results. Although the studies were evaluating common health outcomes, many studies still showed an association after control for known confounders.

Comment 8:

5. Statistical Considerations

Statistical analyses of the potential effects of bias or confounding factors are part of addressing the significance of an association, or lack of one, and whether a study is able to detect any effect.

Comment: Most ETS studies report selective subgroup analyses. Many exposure definitions, combinations and data transformations are explored but not reported. This should be limited by prior commitment to a particular exposure definition and analytic strategy, but it seldom is.

It is particularly important to provide detailed analyses of important confounders. It is not enough to show raw and over-all adjusted results. The analysis should show the level of association of each confounder variable with the outcome and ETS exposure. Otherwise it is impossible to interpret the role of the confounders or the adequacy of the definitions and measures used to characterize them.

Response:

Most of the studies in the report carried out careful investigation of potentially confounding variables. These were based on a priori knowledge of the association between the confounders and the disease and exposure, as well as associations between the confounders and the disease and exposure in the individual studies. However, while some studies include a table showing the association between confounders and the exposure and/or disease, others may have left out such tables due to space considerations. When present these tables almost always show an

association between potential confounders and the exposure and/or disease. A description of all these associations would have taken up too much space in the summaries of the studies. Since the references are supplied, anyone who is interested in this data can go to the journal articles directly. Most of the recent studies employ multivariate statistical methods, which can simultaneously control for several confounders. Not all confounders initially considered remain in the statistical models, either because they do not change the effect estimates or they are highly correlated with other confounders which remain in the model. Therefore, the list of confounders in the final models may be smaller than the number initially considered, while providing the same control of bias as a "full" model with all potential confounders. The use of the more parsimonious model will have the benefit of increased precision.

Comment 9:

6. Combining Statistical Evidence Across Studies

Meta-analysis is a means of comparing and synthesizing studies dealing with similar health effects and risk factors. It is intended to introduce consistency and comprehensiveness into what otherwise might be a more subjective review of the literature. When utilized appropriately, meta-analysis can enhance understanding of associations between sources and their effects that may not be apparent from examination of epidemiologic studies individually. Whether to conduct a meta-analysis depends on several issues. These include the importance of formally examining sources of heterogeneity, the refinement of the estimate of the magnitude of an effect, and the need for information beyond that provided by individual studies or a narrative review. Meta-analysis may not be useful in some circumstances. These include when the relationship between exposure and disease is obvious without a more formal analysis; when there are only a few studies of the key health outcomes; when there is insufficient information from available studies related to disease, risk estimate, or exposure classification; or when there are substantial confounding or other biases that cannot be adjusted for in the analysis (Blair et al., 1995; Greenland, 1987; Peto, 1992).

Comment: As described above, meta-analysis is intended to provide a more consistent, comprehensive, and objective estimate of effect. Meta-analysis is not intended to provide tighter confidence intervals for interpreting statistical significance—indeed such a use is improper. More importantly, there are situations where meta-analysis is not recommended. It is certainly not warranted by the many small ETS studies with poor exposure assessment, weak associations, and with uncontrolled bias and confounding.

In section 2.2.1.4. *Assessment of Evidence of Carcinogenicity from Human Data* EPA makes the following recommendation:

In the evaluation of carcinogenicity based on epidemiologic studies, it is necessary to critically evaluate each study for confidence in findings and conclusions as discussed under Section 2.2.1.2.

Instead of applying these widely agreed upon EPA criteria the authors of both reports claim to have considered the following four methodological issues in reaching their conclusions about the ETS epidemiological studies:

1. Sample Size.

The authors claim to have judged the adequacy of the ETS study sample sizes, but the authors never state what they consider to be an adequate sample size to test hypotheses about possible ETS-related health effects. The adequacy of an ETS study sample size can be determined objectively by considering the expected strength of association (based upon previous research—e.g. the pooled relative risk from all previous studies of the same association), the statistical significance (usually defined as α=0.95, two sided), and statistical power (usually 1-β=.80-.90) that will be accepted. A fundamental study design requirement is that a study be large enough (determined by these three parameters) to test, and if warranted reject, the null hypothesis. Failure to meet this basic requirement is a serious study design flaw. A majority of the ETS studies, on each outcome considered in the report, have inadequate statistical power. Studies that are too small to adequately test their primary research hypothesis also could not adequately control for secondary issues such as bias and confounding. Including such studies in meta-analysis does not correct this problem. Instead it simply increases the likelihood that biases in the small studies will reach the level of statistical significance when they are pooled.

Response:

Throughout the document, OEHHA has summarized specific studies and commented on the strength of conclusion that may be made on the basis of those studies individually, including the issue of sample size and the resultant power of the study. However, most often a meta-analytical approach has been used either formally or informally to assess the implications of the data overall. The commentator is not correct in asserting that meta-analytical techniques are unable to correct for inadequate power of individual studies. This is precisely the purpose of such techniques and, provided appropriate precautions are taken, they are generally regarded as successful and appropriate, although sometimes of course not entirely free of controversy. In their discussion of meta-analysis, Rothman and Greenland (1998) state that small studies can be used in a meta-analysis and that "simulations indicate that, for log relative risks, studies with expected cell sizes as small as four can be large enough for practical purposes."

Comment 10:

2. Potential Confounding.

The authors claim to have evaluated the studies for possible confounding, but do not state any objective criteria for judging the adequacy of the study methods to control for confounding. While weak epidemiological associations are, in general, more likely to be the result of confounding, the authors claim that the weak reported ETS associations are unlikely to be the result of confounding.

The authors do not list the known or suspected potential confounders that should be considered when studying each outcome, nor do they estimate the strength of association of each risk factor with both the primary disease outcome and ETS exposure. The list of potential confounders considered and omitted by each study should be stated, along with a discussion of both the adequacy of the methods used to measure each confounder, and the power of each study to adequately adjust for potential confounding.

Response:

OEHHA has described those confounding influences and the methods used to address them, which are important to the evaluation of the studies in isolation or in the context of the overall range of data available. The issue of confounding has also been addressed previously (see OEHHA's responses to comments 3 and 8). The question of "strength of association" as a decision criterion separate from underlying statistical significance has been discussed previously (see OEHHA's response to comment 2).

The data on the association between active smoking and lung cancer is well accepted, present a clear linear dose response, and result in the observation that active smokers have 15-20 fold increased risk for lung cancer. The excess risk estimates for passive smoking ranging from 7-30% or more are still in a range that is consistent with corresponding dose related excesses noted with active smoking (Blot and McLaughlin, 1998). As noted in the document and below in response to comment 13, ETS contains much higher levels of some carcinogens than mainstream smoke. Other factors should also be considered when evaluating whether an association may be casual. These include biologic plausibility, consistency of findings across studies, and evidence of dose response. These factors have been considered and strongly support the conclusions of the OEHHA document.

Comment 11.

3. Selection Bias.

The control and elimination of selection bias in ETS studies is central to the validity of the studies. Health-related socioeconomic, lifestyle, and dietary differences between households with and without active smokers tend to favor nonsmoking households. The report should have presented a detailed evaluation of the individual studies, critiquing the methods used to assess and adjust for differences between smoking and nonsmoking households.

The authors of the Draft Report claim to have considered possible effects of selection bias on the ETS studies, but they fail to identify what types of selection bias the individual studies should have addressed. The authors do not identify which studies did, and which did not consider each major type of selection bias. They do not discuss how selection bias should be addressed, nor do they describe any objective standard for assessing how well the ETS studies did in addressing possible selection bias.

Response:

Some individual study descriptions and analytical narratives have been expanded to provide clarification.

Comment 12:

4. Exposure Classification Bias.

It is well established that some self-reported non-smokers, the principle subjects in ETS epidemiological studies, are misclassified active smokers. There is a large body of literature devoted to this one aspect of ETS epidemiological research that is largely ignored in the present report (Smith, 2003; Nilsson, 2001; Jenkins and Counts, 1999; Lee and Forey, 1996). The authors provide a cursory and highly selective review of the topic and claim that recent, as well as earlier, studies demonstrate that smoker misclassification is an insignificant problem. To support this assertion they present active smoker misclassification rates raging from 0.8% to 19.7%, and claim that the true rate is more like 1.2% to 2.6%. In fact, every method used to assess smoker misclassification is prone to error, and is likely to under-estimate the true rate, especially the true rate of former active smokers. Figure 2.1 of the CA/EPA 1997 ETS Risk Assessment indicates that about 17% of self-reported nonsmokers in a California survey were actually active cigarette smokers. This is 10 times the smoker misclassification rate assumed in the present report.

Response:

We did not assume any particular rate of misclassification of smoking status. We weighted more heavily studies with biomarkers of exposure. Furthermore, several studies that examined the effect of misclassification of exposure have found that it lead to an underestimation of the effect

(DeLorenze et al 2002; Johnson et al. 2001; Morabia et al. 1998; Jenkins and Counts 1999), not an overestimation of the effect. This is primarily due to ETS-exposed individuals in the non-exposed groups biasing the results towards the null.

Comment 13:

Instead of presenting a balanced review of the active smoker misclassification problem, the authors focus attention instead on the issue of "background" exposure, and assert that this form of misclassification counterbalances active smoker misclassification. This is certainly not true. Environmental tobacco smoke is thousands of times less concentrated than mainstream smoke, and the theoretical health risk of ETS exposure is, in general, orders of magnitude lower than that reported for active smoking. The amount of bias possibly due to misclassification of background exposure is insignificant in comparison to the bias produced by misclassification of active smoking.

Response:

Misclassification of exposure to passive smoking by limited exposure ascertainment results in referent groups containing people who are or have been passively exposed to ETS. The misclassification of smokers as non-smokers affects a very small percent of the nonsmoker referent category in the majority of studies (less than 5%). However, virtually all nonsmokers have been exposed to ETS, particularly in the past when smoking was more prevalent and there were no restrictions on smoking in the workplace, at schools, or in public places. Thus, you have practically speaking a referent category that may have a stray light smoker but almost 100% of the people in referent groups in studies with poor ascertainment of exposure have had at least some exposure to ETS and in many cases significant and long-term exposures. Johnson notes in a letter published in JNCI (2001, 93:720) that Fontham et al. (1994) found that 64% of never-smoking women in the U.S. reported ETS exposure in childhood, 14% reported adult nonspousal household exposure, 24% reported social exposure, and 60% reported exposure at work. The majority of these exposures occurred over many years. This implies that the referent categories of non-exposed can in fact be highly contaminated with exposed individuals if the study only assesses spousal exposure. Nearly all studies that utilize a non-active/non-passive referent population in which an attempt has been made to quantify the estimate of ETS exposure from numerous sources (not just spousal) find significant associations with breast cancer in at least some age or susceptibility groupings for both active and passive smoking (Figure 7.4.2).

The commentator's concern stems in part from the erroneous assumption that ETS is essentially diluted mainstream smoke. There are significant differences in chemical composition between mainstream and sidestream smoke including the relative amounts of specific carcinogens. 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. Hundreds of 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. Evidence from various sources, including biomarker studies (Crawford, 1994; Tang, 1999), suggest that contrary to the comment's assertion, the extent of exposure to carcinogens and other harmful chemicals from ETS can be considerable, and is in fact at least contiguous to, or even overlapping, the range of exposures experienced by moderate active smokers. In view of these facts, the comment as to the low risk from ETS and the insignificant impact of background exposure misclassification appears untenable. Even if it is considered that the typical exposure to tobacco smoke components is lower than that experienced by a regular active smoker, the commentator's assumption that "theoretical health risk of ETS exposure is … orders of magnitude lower than that reported for active smoking" not only exaggerates the difference in exposure, but also assumes a linear dose response for all health risks. As detailed in OEHHA's report, and elsewhere in these responses to comments, although for some end points (e.g. lung cancer risk) the dose response appears relatively linear in the range of interest, this is by no means the case for certain other end points (e.g. cardiovascular effects, breast cancer risk).

Comment 14:

SECTION II : Sudden Infant Death Syndrome.

Comment: The Draft Report repeats the 1997 conclusion that there is adequate epidemiological evidence of a causal relationship between postnatal ETS exposure and SIDS, and claims that the evidence has been strengthened by more recent studies. I believe that this conclusion is not supported by either the previously published research or by the more recent studies.

Epidemiological studies that have measured actual infant ETS exposure have not reported an increased risk of SIDS. Bias and confounding are major influences in the ETS / SIDS epidemiology. Prenatal maternal smoking is a powerful confounding influence in SIDS research. In addition, misclassification of active maternal smoking and exposure to approximately two dozen other SIDS risk factors has not been ruled out by any epidemiology study. The newer studies have not adequately ruled out bias and confounding, and provide inconsistent evidence on an ETS / SIDS association.

Response:

Active maternal smoking in pregnancy is an accepted risk factor for SIDS. Thus in studies of SIDS and maternal exposure to ETS during pregnancy, the misclassification of an active smoker as ETS-exposed could bias the risk estimate upwards. However, while the risks of SIDS from postnatal ETS appear to be higher if the mother smoked during pregnancy, postnatal ETS exposure is a risk factor for SIDS independent of maternal prenatal smoking. It is the effects of a neonate's postnatal ETS exposure rather than the mother's prenatal ETS exposure upon which our assessment is based.

Comment 15:

As discussed below, the study with both the most objective measures of postnatal ETS exposure from all sources, and the most design control over confounding by maternal smoking, did not find a link between postnatal ETS exposure and the risk of SIDS (Dwyer *et al*. 1999).

Epidemiological studies have reported that maternal smoking, the most frequently used proxy for childhood ETS exposure, is associated both with SIDS and with many other SIDS risk factors. For this reason, the maternal smoking / ETS / SIDS association is confounded, and can not be readily interpreted. In addition, it is not clear whether any of the many SIDS risk factors that have been reported, with the exception of prone sleeping position, actually is a direct cause of SIDS. Prone sleeping has not only been associated with SIDS, but interventions designed to modify prone sleeping have successfully reduced the risk of SIDS. No other candidate risk factor comes close to this standard of establishing cause and effect.

Statistical methods are routinely used to "adjust" SIDS study results for the effects of confounding by competing risk factors. Such adjustment is often only an illusion. This is clearly the case in SIDS studies that claim to "adjust" maternal postnatal smoking for maternal prenatal smoking. Maternal pre- and post-natal smoking habits are very highly correlated (a condition known as multicollinearity) so the residual (adjusted postnatal) smoking / SIDS association is not a stable measure of effect.

Problems with statistical adjustment also arise when risk factors are not precisely measured (which is often the case), and/or when they are only indirectly associated with one another or

with the outcome under investigation. In either case observed association will underestimate true associations, and statistical adjustment can only partially control for the effects of confounding. Such measurement problems arise when risk factors are correlated with socioeconomic status (SES). This is because SES is consistently and significantly, but weakly, associated with the risk of SIDS through the action of some unknown factor(s). Socioeconomic status is also consistently and significantly, but weekly, associated with both parental smoking and with childhood ETS exposure. Statistical adjustment of the parental smoking / SIDS association for SES will not fully "control" for confounding by the unknown factor(s). In other words, the adjusted ETS association will still be due, in part or entirely, to confounding. In fact, statistical adjustment for SES may have no effect at all on the parental smoking / SIDS association, or if there are negative associations among some of the risk factors, it could even cause the parental smoking / SIDS association to rise.

At the present time it is not clear that an ETS / SIDS association even exists, let alone that there is a causal connection between the two. More and better epidemiological research is needed to shed light on a possible role of ETS exposure in the etiology of SIDS. Studies are needed that very carefully attend to the complex problems of bias and confounding, and that provide objective measures of ETS exposure. Given the extensive confounding between maternal smoking and infant ETS exposure, future ETS / SIDS studies must focus on nonsmoking mothers. This design requires verification that the mothers are not misclassified former or current smokers. Since recall bias is likely in SIDS case-control studies that collect retrospective questionnaire data, only prospective designs that collect and confirm smoking status, and other risk factor exposure data, prior to the SIDS birth and death are reliable.

Response:

With respect to the other unspecified risk factors to which the comment refers, many studies have found associations while controlling for at least the more significant risk factors. For example, Brooke et al (1997) reported elevated risk associated with maternal (OR 5.05, 95% CI 1.85; 13.77), paternal (OR 2.12, 95% CI 0.99; 4.56) or both (OR 5.19, 95% CI 2.26; 11.91) smoking after controlling for over 20 risk factors. Some of these factors were specific to the infant, such as gender, birth weight, gestational age, breast feeding, initial sleeping position, changes in sleeping position at night, waking in a sweat, symptoms and drug treatment. Others captured familial factors such as maternal age, marital, educational and social status, sleeping with parents, and previous births and infant deaths. Characteristics of the infant's environment were considered as well such as use of cot bumpers, mattress use history, and swaddling.

Comment 16:

Comments on newer studies—

Milerad et al. *1998.*

1. No control for maternal prenatal smoking in this study;

Response:

This study investigated whether there was ETS exposure around the time of death by comparing the pericardial fluid cotinine between SIDS and non-SIDS infants. In this study, elevated cotinine and SIDS were significantly correlated. Whether or not maternal prenatal smoking contributed to the infant death is a separate issue.

Comment 17:

2. Inconsistent results for cotinine comparisons between SIDS versus accidental deaths (no cotinine difference) and SIDS versus infection deaths;

Response:

In Milerad et al (1998), the pericardial fluid was assayed for otinine in babies who gad died iof either SIDS, infections, or accidents. There was a significant difference in pericardial fluid cotinine concentrations between SIDS victims and those dying from infection with SIDS victims having higher levels. In this study, though there was not a statistically significant difference between the pericardial fluid cotinine concentrations between SIDS victims and accident victims. We cannot say why this is true other than it has been noted that people who smoke are more often involved in auto accidents than nonsmokers, and thus children of parents who smoke may be over-represented in auto accidents.

Comment 18:

3. Reduced ETS exposure of infants with infections would be expected -- concerned parents would not be likely to smoke near a sick child.

Response:

It is also possible that earlier ETS exposure contributed to the illness from which the infant ultimately died. It is true that the study does not allow one to make that determination.

Comment 19:

Rajs et al. 1997.

Poorly controlled study. Inconsistent results do not support an ETS / SIDS association.

Response:

While the limitations of the study preclude conclusions regarding the pre- versus postnatal smoke exposure, the study nevertheless supports an association between SIDS and postnatal ETS exposure.

Comment 20:

McMartin *et al*. 2002. Inconsistent cotinine and nicotine results indicate unreliable smoking status data. Study can not account for prenatal maternal smoking.

Response:

We agree with this assessment of this study's limitations.

Comment 21:

Recent ETS exposure may be correlated with cause of death due to recent reduction in exposure of sick infants.

Response:

It is not clear to what this comment refers.

Comment 22:

Alm *et al*. 1998. This study can not separate maternal prenatal and postnatal smoking effects.

Response:

Agreed.

Comment 23:

Mitchell *et al.* Four papers published by Mitchell and colleagues (Mitchell *et al.,*1991; Mitchell *et al.,*1993; Mitchell *et al.,*1995; Mitchell *et al*. 1997) are treated by OEHHA reviewers as if they

were independent when in fact the were not separate studies. Instead they comprise one interim report, and three subsequent publications all stemming from the same SIDS case-referent study.

Response:

The methods sections of the 1993 and 1997 papers indicate the data were collected on infants born during different time periods: 1987-1990 vs 1991-1993. Thus, they can be considered two separate studies.

Comment 24:

The Mitchell *et al*. study design can not separate prenatal and postnatal maternal smoking effects. Mitchell *et al.* reported in 1993 that postnatal smoking by the father did not increase the risk of SIDS when the mother was a nonsmoker, (OR=1.00; 0.64-1.56).

Response:

The authors suggest but cannot prove that this is due to fathers being less likely to smoke around the child if the mother is a non-smoker. In view of these uncertainties and the wide confidence limits on the odds ratio, the result for postnatal paternal smoking in this study should be seen as inconclusive rather than negative.

Comment 25:

In the 1997 study the paternal smoking association is not limited to nonsmoking mothers and can not be interpreted as "independent of prenatal smoke exposure."

Response:

The comment is correct that the estimation of SIDS risk from paternal smoking did not exclude maternal prenatal smoking. It is possible that while paternal smoking in addition to maternal smoking more than doubles the SIDS risk associated with maternal-only smoking (OR 10.09, 95% CI 5.89; 17.337 vs 4.15, 95% CI 2.05; 8.38), this may represent a dose-dependent exacerbation of the effects of maternal prenatal smoking.

Comment 26:

Anderson and Cook (1997) published a review and quantitative meta-analysis of the relationship between postnatal ETS exposure and the risk of SIDS. Their review provides little in the way of description and analysis of the methods and quality of the individual studies. Their reliance on

statistical pooling, with no attempt to rate study quality or interpret possible sources of bias and confounding, is a serious weakness of this review. Meta-analysis cannot correct for the effects of bias or confounding or any other problem in the research methods or data. By ignoring systematic problems such as the extremely high correlation between maternal prenatal and postnatal smoking, the authors ignore serious methodological problems and over-interpret the results of their meta-analyses.

Response:

It was in recognition of the correlation between pre- and postnatal smoking that Anderson and Cook performed a sub-analysis based on studies in which prenatal smoking was absent or controlled. The sub-analysis found a statistically significant elevated association between ETS exposure and SIDS.

Comment 27:

Instead of providing a critique of individual studies, listing potential confounding factors addressed and omitted, and rating the adequacy of the methods, the authors make only general comments about groups of studies. They note, for instance, that eight of nine studies with data on postnatal maternal smoking also provide data on prenatal smoking. They do not explain that it is safe to assume the great majority of maternal smokers in all SIDS epidemiological studies smoked both prenatally and postnatally, whether or not the information was collected. The authors go on to state that four studies "controlled" their postnatal smoking analysis for prenatal smoking, but reference only three studies (one study, Schoendorf, 1992, provided separate odds ratios for black and white cases). In fact, such statistical "control" is not meaningful because nearly all of the mothers smoked both before and after giving birth. Even assuming accurate retrospective questionnaire exposure information (which is unlikely to be a valid assumption), any possible postnatal ETS effect would be hopelessly confounded with prenatal maternal smoking and all of the SIDS risk factors associated with prenatal smoking. Attempts to control statistically for such confounding would be expected to yield unpredictable results.

The results reported in these studies, as expected, are unpredictable. Anderson and Cook note that while five of the studies report greater unadjusted odds ratios for postnatal maternal smoking than for prenatal maternal smoking, three of the studies report just the opposite, and one study reports only that the effect of postnatal exposure was not significant. The only reasonable interpretation of these results is that when there is both prenatal and postnatal maternal smoking, there is no way to separate the possible independent effects of the two on the risk of SIDS. The situation is made more complicated by the many SIDS risk factors that are also associated with smoking.

Blair *et al.* (1996) reported an elevated risk of SIDS when the mother reported that she was a nonsmoker and that the father smoked (OR=3.41; 1.98 to 5.88). However, in that study postnatal smoking by the mother did not significantly increase the risk of SIDS after adjustment for the mother's prenatal smoking. If postnatal ETS exposure actually increases the risk of SIDS, then

these contradictory findings do not make sense because postnatal smoking by the mother is a far more important source of infant ETS exposure than is postnatal smoking by the father and other family members.

Response:

We believe this apparent contradiction arises from the following passage regarding multivariate analysis in the results section. "When we considered parental estimation of the infant's daily exposure to tobacco smoke as a postnatal marker for smoking, this marker was significant when we controlled for other factors (P = 0.008)." The wording suggests that postnatal exposure to ETS from whatever source, be it maternal, paternal or other, significantly elevates SIDS risk. It does not specify only maternal postnatal smoking as the source of ETS, and at this point in the analysis includes cases with and without maternal prenatal smoking. "If maternal smoking during pregnancy was added to the model, however, the postnatal marker lost its independent effect (P = 0.1601). This may be explained by the strong correlation between maternal smoking during and after pregnancy." This suggests that maternal prenatal smoking is more important than postnatal ETS from any source for SIDS risk, an observation supported by other studies. However, it doesn't compare the relative effects from maternal postnatal smoking with ETS from other sources so the findings are not necessarily contradictory. That postnatal ETS increases the risk of SIDS was indicated in the last line of that section ("The additive effect of smoking in pregnancy and postnatal exposure was significant (2.93; 1.56 to 5.48)."), and in the dose-dependent increase in SIDS with increasing daily ETS exposure. From this study it is clear that infants with prenatal smoke exposure are at greater risk of SIDS following postnatal ETS exposure than are infants exposed solely to postnatal ETS, but both groups are at significantly higher risk than are children with no smoke exposure at all.

Comment 28:

Dwyer *et al.* (1999) provide detailed and objective cotinine data on the contribution of both maternal smoking and smoking by other adult residents to postnatal ETS exposure and to the risk of SIDS. The authors state "Although they were predictors of infant urinary cotinine, a history of smoking by other adult residents and whether others smoked in the same room as the baby were not significantly associated with SIDS."

Response:

The data on urinary cotinine are hard to interpret since they are not corrected for volume and dilution effects could lead to spuriously high or low estimates. It is thus uncertain how much ETS exposure from non-maternal sources infants actually received.

Comment 29:

Concerning postnatal smoking habits of the mother, the authors go on to state "Good maternal smoking hygiene (i.e. not smoking in the same room as the baby) was an important independent predictor of lower cotinine levels, decreasing cotinine levels by approximately one half, but was not associated with SIDS." This study reported that SIDS was associated with maternal smoking status (overall prenatal maternal smoking adjusted OR=2.58, 1.14 to 5.79; overall postnatal smoking adjusted OR=2.50, 1.13 to 5.49). However, the authors state "As in previous retrospective studies, we found a positive association between the mother's smoking and risk of SIDS but, as in many other studies, this could not be separated from prenatal maternal smoking because behavior was similar before and after birth."

Response:

The comment is correct in that the infants in this analysis had prenatal as well as postnatal smoke exposure. The study was included to show that altered lung morphology was more prevalent among SIDS victims with smoke exposure than among SIDS victims without. While this study did not demonstrate that ETS caused these changes, it is plausible that altered structure of smoke-exposed infants' lungs makes them more susceptible to subsequent ETS exposure.

Comment 30:

Elliot *et al*. (1998) did not conduct a study of ETS exposure. It is misleading to suggest that this maternal smoking study portrays plausible ETS effects.

Response:

The study by Elliot compared airways of SIDS infants who had been exposed to maternal smoking with airways of infants who had died of non-SIDS causes and who were not exposed to smoke. A thickening of the walls of the large airways was observed among the smoke-exposed SID infants compared to the non-SIDS cases. While the study could not distinguish the effects of pre- vs postnatal smoke exposure, it nevertheless suggests a plausible mechanism by which

infants with airways altered by exposure to maternal smoking would be more susceptible to subsequent ETS exposure.

Comment 31:

Thornton and Lee (1998) review 28 SIDS related studies published between 1966 and 1996. Table 4.1 omits this review, yet it includes the much smaller and less ambitious review by Anderson and Cook (1997). This discrepancy should be corrected. Parts of the Thornton and Lee review are described and selected data from the review are reported in Tables 4.3 and 4.4. Thornton and Lee demonstrate that statistical adjustment of SIDS / tobacco smoke studies for the effects of other SIDS risk factors has an unpredictable, and often a large effect on reported associations. The number of possible confounding risk factors considered by the 28 studies ranges from nearly two dozen to none. The authors' conclusion that there appears to be an association between the risk of SIDS and tobacco smoke exposure is not a conclusion regarding ETS exposure.

Response:

OEHHA disagrees. Thornton and Lee state: "When taken at face value, the data…indicate a strong association between maternal smoking during pregnancy and the subsequent risk of SIDS in the offspring, and a similar association is also seen for maternal smoking after pregnancy." The association between SIDS and maternal smoking after pregnancy is likely due at least in part to ETS exposure.

Comment 32:

The risk of SIDS reported in the studies in the great majority of cases is not independent of maternal prenatal active smoking.

Response:

We agree that in many studies it is impossible to separate the effects of maternal pre- and postnatal smoking, and children exposed to prenatal maternal smoking do appear to be at greater risk of SIDS when exposed to ETS postnatally. However, the higher risk of SIDS among ETS-exposed children of nonsmoking mothers (Nicholl & O'Cathain, 1992; Blair et al., 1996; Brooke et al., 1997) supports an independent effect of postnatal ETS exposure.

Comment 33:

The animal studies reviewed in the report demonstrate tobacco-related effects that occur after unusual modes of exposure and/or at very high levels of exposure. Since the studies do not involve ETS exposure at realistic environmental levels they do not provide a biologically plausible mechanism linking ETS exposure to SIDS.

Response:

It is true that the nature and route of exposure in many animal studies may differ in critical respects from human smoke exposures. However, to the extent that the results from animal studies parallel observations in human SIDS cases, a plausible mechanism may be inferred. A case in point is the study by Slotkin et al. (1999) in which fetal exposure to nicotine at levels approximating moderate, heavy, and no smoking in humans was followed by postnatal exposure to nicotine. Pre- and/or postnatal nicotine exposure resulted in reductions in muscarinic type 2 receptors in the brainstem areas regulating cardiorespiratory functions - similar to that seen in SIDS victims.

Comment 34:

SECTION III : Lung cancer.

The Draft Report concludes, as did the 1997 report, that ETS is a cause of lung cancer, and states that the evidence regarding a causal relationship has been strengthened by more recent research. In my opinion just the opposite is the case. Only the IARC study by Boffetta *et al*. (1998) has both the size and necessary methodological improvements to add significantly to our understanding of the possible role of ETS in the etiology of lung cancer. The IARC study is the most carefully conducted ETS / lung cancer study to date. It underwent years of planning and development, including validation studies of its questionnaires and laboratory methods. It was designed to address questions of bias and confounding more carefully and fully than was possible in the study by Fontham *et al*. (1994), or by any other earlier ETS / lung cancer epidemiology study. The results from the IARC study are not realistically evaluated in the Draft Report. As discussed below, the IARC study does not support the Draft Report's conclusion that ETS increases the risk of lung cancer.

Response:

OEHHA has described the IARC study (Bofetta et al., 1998) and its published components in detail in the report. In this comment only the negative findings are noted: the fuller description in OEHHA's report is quoted to clarify the overall findings:

> "The large multicenter IARC study (Boffetta et al. 1998) did not find a trend with ETS exposure for three of four matrices; duration (years), average exposure (cigarettes/day), or cumulative exposure (pack-years). However, ETS exposure duration estimated in hours/day × years exposed was suggestive of a dose-response relationship (P for trend 0.03)."

*The commentator states "*In particular, the IARC study reports that the most convincing and widely used measures of cumulative ETS exposure are not significantly associated with lung cancer. In fact, the study results indicate that a majority of ETS exposed cases had lower risk than those who were unexposed to ETS (non-significant).*" OEHHA does not agree with the commentator's assertion nor did the authors of the report. They state "*When taken together, our results on exposure to ETS during adulthood are in agreement with the available evidence and, in particular, with large studies from the United States… The risk from ever exposure to spousal ETS was consistent with the combined available evidence from European studies, but it was lower than some previous estimates- a result that could be explained by the large number of subjects whose exposures to ETS ended several years earlier.*" However, the ability to detect significant relationships was limited since the sample size "* was based on an expected difference in risk from ETS exposure that was greater than that which we observed.*" The resultant values, which often showed elevated but not significant risk values, must be interpreted in light of this. Nonetheless, higher values and significant trends in dose response relationships were noted with the combined indicators of spousal and workplace exposure. The p value for trend for combined workplace and spousal exposure "duration of exposure (hours/day x years)" was 0.01 for all subjects and 0.03 for women It is also worth noting that background ETS exposure is significantly higher in Europe than in the U.S. due to the considerably higher smoking prevalence there.*

OEHHA's report also details several problems with the analysis of the overall data from the multicenter study, and contrasts these with the conclusions that may be drawn from those reports on the component studies that have been published to date.

Notwithstanding the commentator's concerns, IARC's recent overall evaluation by their expert panel (which included a representative of the multicenter study team) found evidence for a significant association between exposure to ETS and lung cancer. As noted elsewhere, OEHHA

is not bound to follow IARC's conclusions unquestioningly, but seriously considers IARC's views.. In this case we agree with their evaluation, and view it as adding support to the previously accepted (Cal/EPA, 1997) conclusion that ETS exposure is associated with lung cancer.

Comment 35:

While some earlier epidemiological studies did certain things very well, no earlier study had the size and statistical power to make a convincing case that it had moved the field forward. Most of the dozens of small ETS / lung cancer studies that have been conducted, both before and after 1997, are so similar in design and methods that they can not claim to offer anything new. As discussed in detail in the heart disease section below, the use of meta-analysis under these circumstances is unwarranted. It cannot provide anything new.

Response:

Meta-analysis is now a well-accepted statistical proceduretha thas proved valuable in identifying real information which was difficult or impossible to discern when looking at individual studies in isolation. It should also be noted that Fontham et al 1991., which is an "earlier" study, was a large U.S. study that did find elevated lung cancer risks using cotinine as a measure of exposure.

Comment 36:

The Draft Report would benefit from careful consideration of a recent editorial on ETS / lung cancer epidemiology in the British Journal of Medicine by George Davey Smith, BMJ 2003;326:1048-1049 (17 May). He notes that:

"The considerable problems with measurement imprecision, confounding, and the small predicted excess risks limit the degree to which conventional observational epidemiology can address the effects of exposure to environmental tobacco smoke."

"Misclassification is a key issue in studies of passive smoking."

"Confounding is clearly important, and individuals exposed to environmental tobacco smoke may display adverse profiles in relation to socioeconomic position and health related behaviours."

"As an indicator of exposure to environmental tobacco smoke the smoking status of spouses is a highly approximate measure. This will lead to the risk associated with environmental tobacco smoke being underestimated. Conversely misclassification of confounders can lead to statistical adjustment failing to account fully for confounding, leaving apparently "independent" elevated

risks that are residually confounded. Methods of statistically correcting for misclassification both in the exposure of interest and in confounders exist, but they are highly dependent on the validity of assessments of measurement imprecision."

The editorial proposes a possible way to deal with the uncertainties that accompany low risk, indirect, ETS epidemiology:

"Genetic polymorphisms that are associated with poor detoxification of carcinogens in tobacco smoke have been identified. The distribution of these polymorphisms in the population will not be associated with the behavioural and socioeconomic confounders that exposure to environmental tobacco smoke is. Among people unexposed to the carcinogens in environmental tobacco smoke there is no reason to believe that the detoxification polymorphisms should be related to risk of lung cancer. However, among those exposed to environmental tobacco smoke a decrease in the ability to detoxify such carcinogens should be related to risk of lung cancer, if exposure to environmental tobacco smoke is indeed responsible for increased risk of lung cancer. One study showed that a null (non-functional) variant of one such detoxification enzyme, glutathione S-transferase M1, was associated with an increased risk of lung cancer in non-smoking women exposed to environmental tobacco smoke, but not in non-exposed non-smoking women (Bennett *et al*. 1999). A later study failed to confirm this finding,(Malats *et al*. 2000) reflecting one limitation of Mendelian randomisation, which is that large sample sizes are required to produce robust results. However, this is a promising strategy if we really want to know whether passive smoking increases the risk of various diseases."

While no single molecular epidemiology study is capable of providing all of the data needed to settle the issue, there will eventually be solid data on the mechanisms that cause about one in ten life-long active smokers to develop lung cancer, and not the other nine. Only then can ETS / lung cancer epidemiology studies be conducted that are not subject to the effects of bias and confounding too subtle for current designs to control, yet great enough to produce the very weak associations that are reported.

Response:

OEHHA thanks the commentator for providing this abstract of an interesting and provocative editorial. OEHHA is familiar with this citation, but did not review it in the present update document. As noted in the introductory remarks to both this and the 1997 document, the intent was to concentrate on new primary data sources and new statistical methods, rather than to include review articles or editorials. The selective quotations from Smith (2003) raise a number of points of concern or future interest, with which OEHHA does not disagree. Some of these are indirectly addressed in the OEHHA document. In contrast to the view expressed in the comment, it does not appear to OEHHA that the materials quoted detract from the conclusion of our draft report. In fact, some of the points related to misclassifiction of exposure tend to bias towards the

null and underestimate the risk Finally, it is important to note that the problems noted in this editorial do not obviate the consistent findings of elevated lung cancer risk across many studies..

Comment 37:

The Draft Report presents in Part A, Appendix *A "List of known ETS constituents*", a list of constituents of mainstream and sidestream smoke rather than constituents of ETS. This is a misleading title that should be corrected. Table III-1 and Table III-2 list constituents that have actually been at least qualitatively measured in ETS. The Draft Report also notes that some chemical constituents of sidestream smoke are produced in higher concentrations than in mainstream smoke. This is true, but it is no basis for concluding that risk estimates based upon spousal smoking associations are plausible when compared to active smoking risk estimates. That "cigarette equivalent" exposure comparison should be based upon a comparison of actual mainstream smoke and ETS exposure levels, not upon a comparison of constituent levels in mainstream smoke with levels in fresh, distilled and concentrated sidestream smoke. Environmental tobacco smoke is aged, diluted, and dissipated in natural environments and is not the same as sidestream smoke. Most sidestream smoke constituents are transformed or reduced to such low concentrations that they are no longer quantifiable in ETS.

Response:

[ARB is responding to this comment.]

Comment 38:

The Draft Report also makes a number of errors and omissions in the ETS / lung cancer section. A serious error is the way in which the text and Table 7.2A deals with the separate subsets of the large IARC study by Boffetta *et al*. (1998). The text discusses the sub-studies as if they were all independent. A casual reader may not understand from the brief references to Boffetta in the text summaries that data from the by Nyberg *et al*., Zaridze *et al*., and Kreuzer *et al*. studies are already included in the IARC data. Table 7.2A is even more likely to be misinterpreted as listing independent studies and data. Many readers will not see, or will not understand how to interpret, the disclaimers in the text and in the notes about these studies under Table 7.2A. If these studies are included in both places in the final draft, it should be made very clear in both places that they are subsets, and must not be interpreted as providing independent data. As discussed below, it should be explained to the reader that the three are self-selected subsets of the IARC study, and are not representative of the full study.

Response:

OEHHA doubts that the "casual reader" has got this far into such a technically intensive document. As noted in the comment, the relationship between the component studies and the overall report by Boffetta et al. (1998) is noted where appropriate.

Comment 39:

Both the publication history and the presentation of these studies in the Draft Report provide a rare example of publication bias—a case in which the information needed to understand the degree of bias is available to the informed reader. The IARC study included twelve cooperating research centers. IARC developed the study methods, pooled data from all the centers, and was responsible for the final joint report. So far only three of the twelve centers have published separate reports--the centers where Nyberg *et al*., Zaridze *et al*., and Kreuzer *et al*. conducted their sub-studies. Nine centers have not reported their subsets of the IARC study data. Each time a subset of the IARC data is analyzed and reported there is an opportunity to capitalize on chance associations not present in the full data set. That fact alone is a problem, but it is also likely that the data subsets that do get published separately reflect *post hoc* analyses. This makes the subset reports even less likely to be objective and representative. It is very likely that the nine centers that did not publish separate results had more null or negative ETS / lung cancer associations than did the three that published separately. This is not just speculation. The IARC combined study reports null trend tests for every ETS exposure metric employed except for the statistically significant protective trend for childhood ETS exposure (increasing exposure / decreasing risk of lung cancer). The combined study also reports numerous negative and null individual ETS / lung cancer associations. This could only have come about if many of the nine centers that did not report separately have null or negative data.

Response:

OEHHA has discussed the IARC multicenter study and its components in detail in the report, and has noted the effect of diversity in populations and exposure measures between the various contributing centers there and in earlier responses to theses comments. OEHHA agrees that some of the smaller center sub-studies may quite likely have produced locally null results, due to smaller populations, difficulties in estimating exposures or outcomes, and other site-specific problems. It appears to OEHHA that these local problems may well have diluted the conclusions of the overall analysis by Boffetta et al. (1998), making it all the more appropriate to consider both this analysis and the major contributing studies where such difficulties were successfully avoided or addressed.

Comment 40:

The IARC study by Boffetta *et al*. is the largest and by far the most important ETS / lung cancer epidemiological study that has yet been conducted. It is not a perfect study, but it has better ETS / lung cancer epidemiological data than any other study. This is because the study was designed to address many of the earlier criticisms, especially active smoker misclassification. The study methods underwent extensive development and validation prior to the start of the study, and it is large enough to make use of its improved data on smoker misclassification and confounding.

None of the many smaller ETS / lung cancer studies that have been conducted have the statistical power to deal as effectively with these problems as the IARC study. Pooling the many smaller studies is not an answer when the underlying study design is subject to systematic bias.

Response:

OEHHA agrees that the IARC study represents an important addition to the literature on the health effects of ETS. As will be concluded from the authors' summary analysis that was quoted in an earlier response, its conclusions with regard to lung cancer are consistent with those of other studies and with the earlier and widely accepted conclusions of the OEHHA 1997 report. OEHHA therefore considers it justifiable to regard both these results, and other findings, as supportive of and strengthening that earlier conclusion.

Comment 41:

The description of the IARC study provided by the report does not make it clear that female lung cancer cases accounted for nearly 80% of the IARC study cases (508 females versus 142 males). This is important not only because of the greater statistical power, it also provides the most direct comparison of the IARC study results with the results of other studies and meta-analyses, all of which deal exclusively or primarily with female cases. In particular, the US EPA (1992) ETS / lung cancer meta-analysis rejected data for males on various grounds, asserting that the male data were not as robust as the female data (the pooled male relative risk also happened to be lower than the pooled female relative risk at that time). They then applied the pooled female ETS / lung cancer risk to all males for their population risk analysis. The current report should point out that the IARC female data are inconsistent with the US EPA risk analysis logic and methods. Even applying the unprecedented 90% confidence interval used in the US EPA report, the IARC female ETS / lung cancer relative risk is not statistically significant. I do not object to listing all of the IARC results, for both sexes separately and combined, but the real significance of the female results as a check on other studies and methods of analysis is not even discussed in the report.

Response:

The earlier studies' concentration on results in females reflects an ability to accurately identify nonsmokers exposed to ETS among females, but not males, in some cultural environments. IARC was studying different cultural groups where such distinctions may not apply consistently. OEHHA considers that these cultural factors outweigh any conclusions that could be drawn as regards the underlying biological processes, or the consistency of the epidemiological results.

As noted earlier in these comments and in the introduction to OEHHA's recent document, the purpose of that document is to review new original data that have appeared since the previous report in 1997. Review or criticism of the 1992 US EPA report meets neither of those qualifying conditions. OEHHA has reviewed the data from the IARC multicenter study and its components in the recent report, and further in responses to these comments. Additional work on improving the attributable risk estimates provided by OEHHA for lung cancer and other endpoints (which in some cases use methodology similar to EPA's earlier estimates, but are not intended as a comment on that analysis) has been undertaken in response to these and other comments, and is presented in the revised version of the OEHHA report.

Comment 42:

It is also important to note that inconsistencies among many of the reported IARC study trend tests and tests of multiple related ETS exposure measures undermines any simple interpretation of the risk estimates reported in some of the highest exposure categories. The Draft Report tends to discuss these higher risks as if they make dose-response "sense", even when in fact there is no dose-response observed. In fact, the highest levels of spousal smoking in the IARC study are likely to be associated with the highest levels of smoker misclassification and confounding by other lung cancer risk factors. Numerous reports describe such correlated effects of bias and confounding in ETS exposure studies. Efforts made by IARC to control these factors may not have been as successful in extreme cases as they were on average.

Response:

OEHHA interprets differences in test results between different exposure measures as indicative of differences in precision of those measures, rather than assuming that they arise from unspecified and unidentified effects producing bias and confounding. OEHHA prefers to adopt the hypothesis providing the most economical basis of assumption, and one which does not include multiple unidentified or unknowable factors.

Taking the data as a whole (not merely the IARC study), it is apparent that there is a dose response in the sense that higher and longer exposures produce greater effects. However, it has been pointed out elsewhere in these responses (and in OEHHA's report) that the observed dose response relationship is not necessarily linear for all endpoints. Furthermore, due to the complexities of determining and quantifying ETS exposure, it is difficult to characterize the dose-

response relationship. The fact that it is observable lends credence to the causal association between ETS exposure and lung cancer.

Comment 43:

The Draft Report misstates the importance of active smoker misclassification as a potential source of bias in the spousal smoking / lung cancer study design. First, in section 1.3.1, then again in section 7.0.1.2 it is implied that misclassification of background exposure to ETS is comparable to, and counterbalances, active smoker misclassification. That is clearly not the case. Active smoking involves tobacco smoke exposures two or three orders of magnitude greater than ETS exposure. Any possible bias introduced by background ETS exposure is trivial compared to the bias that may be introduce by active smoker misclassification.

It should also be pointed out that the background exposure adjustment argument involves circular reasoning. It assumes that ETS causes lung cancer in order to prop up the argument that a very weak spousal smoking / lung cancer association stands as proof that ETS causes lung cancer. The observed spousal smoking / lung cancer association is marginal at best. The best study, the IARC study, undermines the causal conclusions drawn by the US EPA and OEHHA.

The Draft Report misstates the importance of misclassification rates reported in the study by Jenkins and Counts (1999). Jenkins and Counts state:

> "Estimated misclassification rates for self-reported lifetime never-smoking females are sufficiently high (2.95% using a discrimination level of 106 ng/ml) that, if used in the Environmental Protection Agency (EPA) risk assessment related to ETS and lung cancer, would place the lower 90% confidence interval (CI) for relative risk at nearly 1.00, i.e., no statistically significant increased risk."

In that study participants knew that they would be asked to provide biological samples to assess their tobacco smoke exposure and to carry devices to monitor their environmental exposure. It is surprising that any subjects tried to conceal their true smoking status under those conditions. The misclassification rates in that study are best viewed as a lower limit for typical epidemiological studies. The Jenkins and Counts study could not detect smokers who quit just for the duration of the study. Neither the Jenkins study, nor any other epidemiological study that has used biological samples to assess cotinine, can detect smokers who have recently quit smoking (because of hospital no-smoking rules, for instance), let alone detect former smokers.

Response:

*The assertion that "*Active smoking involves tobacco smoke exposures two or three orders of magnitude greater than ETS exposure*" appears not to be supported by available evidence. As noted in the report, it appears that for a number of critical carcinogenic and co-carcinogenic*

components and biomarkers, the higher end of exposure to ETS overlaps with the lower end of the active smoking range.

OEHHA has extensively treated the issues of misclassification both in the 1997 report, and in the update and responses to these comments (see for example the response to comment 43 below). OEHHA concluded, along with other authorities such as US EPA and IARC (2004) that although various misclassification issues have been identified, they generally result in bias towards a null result, and the conclusion that ETS exposure is associated with increased lung cancer, in particular, is a robust result.

Comment 43:

Publication bias is largely ignored in the Draft Report. Copas and Shi (BMJ. 2000 Feb 12;320(7232):417-8.) state:

> "A significant correlation between study outcome and study size suggests the presence of publication bias. Adjustment for such bias implies that the risk has been overestimated. For example, if only 60% of studies have been included, the estimate of excess risk falls from 24% to 15%. CONCLUSION: A modest degree of publication bias leads to a substantial reduction in the relative risk and to a weaker level of significance, suggesting that the published estimate of the increased risk of lung cancer associated with environmental tobacco smoke needs to be interpreted with caution."

Response:

In this academic argument, Copas and Shi do not dispute that there is an increased risk of lung cancer due to passive smoking nor do they seriously challenge previous estimates of it's magnitude. In responding to comments regarding possible publication bias in their paper included in Copas and Shi (BMJ, 2000), Hackshaw et al. (BMJ, 2000) recalculated the relative risk estimates from their analysis excluding the six or twelve studies with the largest standard errors, an estimate of small study size, thereby restricting the analysis to studies with smaller standard errors that are less susceptible to increased publication bias. Neither estimate was found to materially differ from the original estimate indicating minimal if any effect of publication bias. A previous examination of the effect of publication bias against statistically nonsignificant results in peer reviewed journals on lung cancer estimates similarly found no effect (Bero et al., 1994).

With respect to publication bias, OEHHA notes that nine of the 12 center specific odds ratios for lung cancer for combined environmental tobacco smoke from the spouse or at the workplace were above 1.0 in the IARC study by Boffetta et al. (Figure 2). Therefore, among the nine centers that did not publish separate reports, six had positive results. Furthermore, since these 12 centers conducted a cooperative study with the same data collection methods and instruments, it is most appropriate to evaluate the results that combined study subjects across centers. The authors stated "although not fully consistent, the differences in the center specific results were – in most cases – not statistically significant, and some random variability is inherent in comparisons between subgroups." Furthermore, there was no clustering of results by aspects of design such as use of hospital-based or community-based controls.

Smoking misclassification was evaluated extensively in a validation study conducted at three of the 12 centers from the IARC study (Nyberg et al., 1998, Cancer Causes and Control, 9: 173-182). They found that only five of 408 index subjects who had never smoked regularly (1.7 percent) were reported by next-of-kin to be former regular smokers. Four of these five subjects had smoked a total of between 18 and 91 packs during their entire lifetimes, while the other one had smoked a total of 390 packs (about 1.1 pack years). An additional three cases and three controls had initially reported less than 400 cigarettes in their lifetime, but next of kin reported that they had smoked between 21 and 78 total packs of cigarettes during their lifetimes and were not regular smokers. It is clear from this validation study that the misclassified smokers actually had very little exposure to active smoking. They had also stopped smoking long ago (4 to 47 years ago). Furthermore, the misclassification was non-differential with respect to lung cancer status, which would tend to bias the results to the null. In fact, excluding the possibly misclassified subjects did not substantially alter relative risks for lung cancer associated with indicators of ETS exposure.

Comment 44:

The study by Enstrom and Kabat (BMJ. 2003) that is based upon the California component of the ACS CPS I study is criticized in the Draft Report for purported study design flaws that are common to all of the ETS studies, including its sister ACS study, the CPSII study. It appears that when a study is positive and can be construed to support the conclusions of the Draft Report such flaws are less important than when the study is null or negative.

Concerning the by Enstrom and Kabat study and the two ACS studies the editorial by George Davey Smith (BMJ 2003) states:

> "Confounding is clearly important, and individuals exposed to environmental tobacco smoke may display adverse profiles in relation to socioeconomic position and health related behaviours. The American Cancer Society's first cancer prevention study was established in 1959, when smoking was much less associated with such factors than it currently is in the United States. It could be argued that this is why smaller risks associated with environmental tobacco smoke are seen in the first, compared to the second, American Cancer Society study (ACS II). In the second study with participants recruited in 1982, women exposed to environmental tobacco smoke had less education than those unexposed, as opposed to the lack of any such gradient in the first study. Similarly among men in the 1982 cohort there was little educational gradient, whereas among men in the 1959 cohort the exposed group had more education than the unexposed group. These figures reflect changing social gradients in smoking among men and women over time. Socioeconomic confounding in the second study would lead to overestimation of the effect of environmental tobacco smoke, whereas there is relatively little confounding in the first study, and what confounding there is could lead to underestimation of the effects of environmental tobacco smoke.

The Enstron and Kabat study can not be ignored. The Draft Report includes separate discussions and table entries for three studies that were subsets of the large IARC lung cancer epidemiological study. It is inconsistent to argue that because this study is a subset of a larger study it can be omitted. This study should be summarized in the text (including the authors' own description of methods, results, and conclusions) and presented in the tables:

> **"**RESULTS: For participants followed from 1960 until 1998 the age adjusted relative risk (95% confidence interval) for never smokers married to ever smokers compared with never smokers married to never smokers was 0.94 (0.85 to 1.05) for coronary heart disease, 0.75 (0.42 to 1.35) for lung cancer, and 1.27 (0.78 to 2.08) for chronic obstructive pulmonary disease among 9619 men, and 1.01 (0.94 to 1.08), 0.99 (0.72 to 1.37), and 1.13 (0.80 to 1.58), respectively, among 25 942 women. No significant associations were found for current or former exposure to environmental tobacco smoke before or after adjusting for seven confounders and before or after excluding participants with pre-existing disease. No significant associations were found during the shorter follow up periods of 1960-5, 1966-72, 1973-85, and 1973-98.
>
> CONCLUSIONS: The results do not support a causal relation between environmental tobacco smoke and tobacco related mortality, although they do not rule out a small effect. The association between exposure to environmental tobacco smoke and coronary heart disease and lung cancer may be considerably weaker than generally believed."

Response:

. OEHHA presented and discussed various of the findings from Enstrom and Kabat in several chapters of this document.*The implication in the comment that because Enstrom and Kabat did not find an association between ETS exposure and lung cancer or heart disease in the California population studied in ACS, that no such association exists for Californians is not supported by the evidence. Enstrom and Kabat's paper is only one of many that have studied ETS exposure and lung cancer and/or heart disease. There is sufficient evidence from other investigations of a correlation between ETS exposure and both lung cancer and heart disease. As is often true in epidemiology, not every study of association between an exposure and disease is going to show a positive result even when the association is fairly strong given the vagaries of exposure ascertainment, particularly with ETS. The study by Enstrom & Kabat (2003) based exposure classification on spousal smoking at baseline in 1959. The study fails to control for other ETS exposures at a time when smoking, and hence ETS exposures were more pervasive. The study also fails to account for changing exposure of the "exposed" group over time, thus creating additional exposure misclassification. Indeed, in a letter to the editor (http://bmj.bmjjournals.com/cgi/eletters/326/7398/1057#32482), Dr. Thun of the American Cancer Society noted:*

"Scientifically, the fatal flaw of the paper is that the information collected on environmental tobacco smoke (ETS) exposure is insufficient to distinguish persons who were exposed from those who were not. When the study began in 1959, no information was collected on potential ETS exposure other on the smoking behavior of the spouse. At that time, exposure to second-hand smoke was pervasive in the United States and virtually everyone was exposed to ETS either at work, in social settings, or in other activities of daily living. Thus, the comparison group of "unexposed" persons whose spouses did not smoke was highly exposed to other sources of ETS, both before the study and during at least the first decade of follow-up. After 1972, the potential for misclassification of exposure was perpetuated and magnified, since no further information was collected on smoking by the spouse or on other sources of ETS exposure during the remaining 26 years of follow-up. Many of the spouses who reported smoking at the start of the study would have quit, died, or ended the marriage, yet the surviving partner was still classified

as "exposed" in the analysis. The long duration of follow-up is a liability rather than a strength of the study with respect to the resultant misclassification of ETS exposure."

Comment 45:

Several studies have been published since the 1997 report that consider possible sources of confounding in ETS epidemiology studies. Trobs *et al*. (2002) investigated both by questionnaires and biochemical analyses whether smokers influence the dietary habits of nonsmokers living in the same household. The study population was a subgroup of the Prevention Education Program in Nuremberg in which 817 adults aged 27-66 years were allocated to one of the four groups: Nonsmokers living with a nonsmoker (Group 1), nonsmokers living with a smoker (Group 2), smokers living with a nonsmoker (Group 3), and smokers living with a smoker (Group 4). RESULTS: The four groups did not differ in the body mass index, the concentration of lycopene, all-trans-retinol, and selenium in plasma. Plasma concentrations of high-density lipoprotein cholesterol, triglycerides, homocysteine, cobalamin, folate, beta-carotene, and alpha-tocopherol showed a gradient to unfavorable levels from Group 1 to Group 4. This trend was also reflected in the reported dietary intake of beta-carotene, alpha-tocopherol, ascorbic acid, fiber, and linoleic acid.

> CONCLUSIONS: "Our data show that nonsmokers living with smokers indulge in less healthy dietary habits than nonsmokers living with nonsmokers. This has to be considered when evaluating the health risks of exposure to environmental tobacco smoke."

Response:

OEHHA has considered that dietary habits may differ in smoking versus non-smoking households. Biochemical markers studied in the dietary studies are not consistently associated with increased risk of lung cancer. Although some argue that elevated levels of dietary antioxidants may be protective, this effect has not been established. In any case, the lower systemic levels of antioxidants in active smokers and those exposed to ETS might well be a biochemical consequence of the exposure, rather than a confounding covariate related to diet. Other negative health indicators such as obesity may actually be negatively correlated with smoking habit and/or smoke exposure. The one lifestyle variable that has been consistently associated with smoking habit is alcohol consumption, which has been effectively controlled for in several recent studies.

Comment 46:

Mao *et al*. (Int J Epidemiol 2001) studied socioeconomic status and lung cancer risk in Canada. They found a statistically significant association between "income adequacy", education, social class, and lung cancer risk.

Forastiere et al. (Environ Health Perspect. 2000) report on "Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas." The authors state that:

> "…Women married to smokers were more likely to be less educated, to be married to a less educated husband, and to live in more crowded dwellings than women married to nonsmokers. Women married to smokers were significantly less likely to eat cooked [odds ratio (OR) = 0.72; 95% confidence interval (CI), 0.55-0.93] or fresh vegetables (OR = 0.63; CI, 0.49-0.82) more than once a day than women not exposed to ETS. Exposed women had significantly higher urinary cotinine than unexposed subjects (difference: 2.94 ng/mg creatinine)."

Response:

Socioeconomic status or related variables such as diet, income or education level have been consistently associated with a wide range of health outcomes both in relation to background incidence of diseases and in studies of responses to adverse environmental exposures. Because of this, epidemiological studies seeking to evaluate such effects routinely control for this relationship, either using SES or its surrogate as a measured covariate, or by using matched exposed and referent populations. OEHHA's evaluation of the studies of lung cancer and ETS exposure shows that the majority of such studies control effectively for this influence. Any residual confounding is by no means sufficient to explain the observed association between ETS exposure and lung cancer.

Comment 47:

SECTION IV : Nasal Sinus Cancer.

The previous OEHHA report concluded on the basis of three studies that ETS exposure is a cause of nasal sinus cancer. Two of the three studies were mortality studies, an outcome measure that the present Draft Report now criticizes (Hirayama, 1984; Zheng, *et al*. 1993). The cohort mortality study by Hirayama (1984) has also been extensively criticized by others (Kilpatrick, 1987; Fleiss, 1990). The Hirayama study reported a significant association between spousal smoking and nasal sinus cancer.

That cohort mortality study also looked at many different causes of death in relation to their defined exposure, so the true meaning of statistical significance in such studies is debatable. The mortality study by Zheng *et al*. was a case-control study. That study reported an improbably high (RR=3.0) risk that was not statistically significant, and there was no dose-response association between spousal smoking and nasal sinus cancer. The third study was a case-control incidence study. It too failed to find a significant association between nasal sinus cancer and ETS exposure. I commented at the time that such sparse and inconsistent data did not warrant the conclusion reached in the report.

There are now four more case-control studies on the possible association of ETS exposure and nasal sinus cancer (now termed nasopharyngeal cancer, or NPC). Three of the four studies are null—that is, they do not report a statistically significant association. In fact, the study by Cheng *et al*. (1999) reports that among non-smokers it found a lower nasopharyngeal risk associated with both childhood ETS exposure (borderline statistically significant), and ETS exposure in adulthood. The fourth study by Yuan *et al*. (2000), which was a case-control study conducted in Shanghai, China reported inconsistent results. They found statistically significant associations between ETS exposure in women but not in men. Thus, the majority of studies on this topic are still null, three of the most recent studies are null, and the fourth has inconsistent results.

These data on ETS exposure and the risk of nasal sinus cancer are still very sparse and inconclusive. They still do not support a conclusion that ETS increases the risk of nasal sinus cancer.

Response:

OEHHA wishes to clarify mislabeling in the text of this update. Nasal sinus cancer was the subject of studies reported in the 1997 document. For this update, no new studies of nasal sinus cancer and ETS were located, and therefore the 1997 conclusion was not altered. The studies included in the update address nasopharyngeal cancer but were presented in a section mistakenly labeled nasal sinus cancer. The document will be changed to reflect this and OEHHA apologizes for the confusion.

Regarding the new section on nasopharyngeal cancer, the results of the Yuan et al. (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although as the comment indicates, in males the confidence intervals include no effect. The study by Armstrong et al. (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood. However, there was a significant association between childhood exposure to

parental smoking and subsequent nasopharyngeal cancer (OR 1.54; p = 0.040). This is consistent with the results of Yuan et al. for females and may indicate a developmental window of susceptibility. More recent studies are considered suggestive of a possible association between childhood ETS exposure and subsequent development of nasopharyngeal cancer.

Comment 48:

SECTION V: Breast Cancer.

The Draft Report concludes that the weight of evidence is consistent with a causal association between ETS exposure and breast cancer. The Draft Report ignores authoritative reviews that have reached the opposite conclusion regarding active smoking and breast cancer. Both the Surgeon General (2001) and IARC (2002) have concluded that the weight of evidence is not consistent with a causal association between active smoking and breast cancer. Okasha *et al*. (2003) recently reviewed the breast cancer epidemiologic literature and conclude: "There are inconsistent results regarding the association between smoking at a young age and breast cancer risk. There is little evidence for an association between passive smoking in early life and breast cancer risk."

In my opinion the weight of evidence is not consistent with an association between ETS exposure and breast cancer.

Response:

There are number of reasons why the conclusions of the Cal/EPA report may differ from other evaluations, such as that recently published by IARC. In the case of the association with breast cancer, we were able to include some studies and meta-analyses which were unavailable to IARC at the time of their report. OEHHA staff and consultants also undertook different (and more extensive) analyses of data than those used by IARC.

Comment 49:

The epidemiological data on breast cancer and both active smoking and ETS exposure are highly inconsistent. With few exceptions, both active smoking studies and ETS exposure studies have inconsistently reported breast cancer associations in a range extending from below rr=1.0 to about rr=1.5. Yet active smoking involves tobacco smoke exposures two or three orders of magnitude greater than ETS exposure, and it includes the highest possible ETS exposure. The case simply can not be supported that ETS increases a breast cancer risk that is not clearly and strongly supported in studies of active smokers.

Response:

Also, please see the response to comment 43.

OEHHA has proposed that a) the observed association between ETS exposure and breast cancer is real and causal and b) that the dose-response for the mammary carcinogenic effect of tobacco smoke is non-linear, especially toward the higher dose ranges associated with active smoking. OEHHA sees this as primarily a data-based explanatory hypothesis which succeeds in unifying to a substantial degree all of the observed epidemiological results, without having to resort to any extraordinary deconstruction of the relevant studies. The converse hypothesis, that there is no such carcinogenic effect of tobacco smoke at any dose level, requires detailed, and individually different, dismissals of a substantial number of studies by assuming unproven statistical imbalances, unidentified confounders, and failure of recognized methods for dealing with confounding and covariance, as well as dismissal of a large number of toxicological studies on individual carcinogens in tobacco smoke. As detailed in the document, and elsewhere in these comments, several independent studies have shown that, when a genuinely non-exposed referent group is used, subjects with exposure to environmental tobacco smoke have an increased risk of breast cancer which is in fact similar to the risk faced by moderate active smokers. One theory which has been advanced to explain this observation is that the higher doses of tobacco smoke experienced by active smokers have an anti-estrogenic effect which may, at least for some women, be sufficient to reduce the risk of (estrogen dependent) breast cancer to a level similar to, or even below, that experienced by those with passive exposure only. It should be apparent that OEHHA is <u>not</u> arguing that, although ETS apparently increases breast cancer risk, active smoking does not. In order to explain the essentially null results of Wartenberg et al., and other large prospective studies where tobacco exposure in the referent group was inadequately determined, it is necessary only that the risk for active smokers be reduced to approximately that experienced by passive smokers (which is, according to other studies, perhaps 1.5 – 2 times higher than that for unexposed women), not to zero.

Comment 50:

The real problem is that such weak associations are below the resolving power of the methods used in the ETS epidemiological studies that have been conducted. Under such conditions, the

advice of Dr. George Davey Smith (discussed in the introduction to my lung cancer comments) is the best course for future research. The most plausible explanation for comparable active smoking and ETS results is the inability of current epidemiological studies to control for bias and confounding. While a majority of active smoking / breast cancer epidemiological studies did try to control for alcohol consumption, which is known to be associated with active smoking and ETS exposure, only about half of the ETS studies collected data on alcohol consumption. And even when questionnaire data are collected on such things as diet, socioeconomic status (SES) and physical activity, considerable misclassification is likely.

Response:

OEHHA has already addressed the commentator's error on characterizing the reported associations as "weak" in the response to comment 10. OEHHA does not agree that the dismissal of all the substantial findings in diverse studies as the result of different and in some cases opposing types of bias and confounding, in spite of the use of effective measures to address these issues in various studies (see OEHHA's response to comment 43), is warranted.

Comment 51:

The failure of null and/or low reported relative risk studies to adjust for socioeconomic status SES is mentioned repeatedly in the Draft Report as a possible negative bias in ETS / breast cancer epidemiological studies. This criticism is selective and misleading. Only one of the studies (Jee *et al*. 1999) claims to have adjusted for SES. However, that study does not state whether the Hollingshead SES Index or some other standardized SES assessment method was used. It is unlikely that the adjustment made any difference in that null study in any event. Marcus *et al*. (2000) is the only other study that adjusted for both education and income, (no attempt was made to classify occupational status) and that study also failed to find an increased risk of breast cancer in ETS exposed cases. Six recent active smoking / breast cancer studies adjusted for education and six did not. Only four recent ETS / breast cancer studies reviewed in the Draft Report adjusted for education, and eight did not.

Response:

Since SES as formally classified is strongly correlated with measures of income and education, it is likely that any of these variables would have a similar effect, whether examined as an independent variable in a multivariate analysis, or when acting as a confounder. Thus any of several surrogate measures for SES (i.e. education) are deemed to adequately reflect SES. In one form or another, most newer studies did indeed consider SES. Sometimes that is not easily determined by a simple reading of the paper.

Comment 52:

The large cohort studies by Wartenberg *et al*. (2000) and Egan *et al*. (2002), which the Draft Report criticized for failure to adjust for SES, are among the least likely to suffer from important SES related biases. The Wartenberg cohort has been criticized for just the opposite problem—it is a convenience sample of middle-class friends of middle-class American Cancer Society (ACS) volunteers. While this composition may limit inferences about the U.S. population, it assures a relatively homogenous SES of study participants. The Egan cohort is even more homogeneous—all of the subjects are nurses. Both of these cohorts achieved better control of possible SES differences through their design than studies that adjust only for income and/or education. Both of these cohort studies also adjusted for a long list of possible breast cancer confounders, including alcohol consumption, and they used a design that is not susceptible to recall bias. The null results from these two large cohort studies alone should have persuaded the authors of the Draft Report that the weight of the ETS / breast cancer evidence does not support causation.

Response:

We agree that in a cohort that is based on common occupation one can assume a relatively homogeneous population regarding SES. We note this in the revised document. As OEHHA noted, the effect of this confounding variable would generally be to generate a bias towards a null result.

OEHHA's analysis of the Egan and Wartenberg studies is presented at length in the document, and discussed in the responses to these and other comments. Briefly, although OEHHA has identified or suggested a number of possible influences on the outcomes of these studies, the major impact is suggested to be misclassification of members of the referent group. In view of this finding, and the positive results in studies that address the problem, the commentator is correct in characterizing the conclusions of these studies as "null" rather than "negative" results. OEHHA's analysis of the overall body of data is consistent with the observations reported by these studies, such as they are.

Comment 53:

The authors of the Draft Report also criticize the cohort study by Wartenberg *et al*. for using breast cancer mortality as an outcome measure instead of breast cancer incidence. While it is true that studying mortality misses cases that are cured or in remission at the end of the study, there is no reason to believe that such missed cases are related to tobacco smoke exposure. In their 1997 report the OEHHA authors did not criticize the Cardenas *et al*. (1997) ETS / lung cancer study, which used the same ACS mortality study data as Wartenberg *et al*. In their 1997

report the OEHHA authors did not criticize the Steenland *et al*. (1996) ETS / heart disease study, which used the same ACS mortality study data as Wartenberg *et al*.

The Draft Report description of the Wartenberg *et al*. study should be replaced by the peer reviewed description published by the authors.

> "BACKGROUND: Several studies have reported positive associations between environmental tobacco smoke (ETS) and increased risk of breast cancer. However, studies of active smoking and risk of breast cancer are equivocal and in general do not support a positive association. To try to resolve this paradox, we examined the association between breast cancer mortality and potential ETS exposure from spousal smoking in an American Cancer Society prospective study of U.S. adult women. METHODS: We assessed breast cancer death rates in a cohort of 146 488 never-smoking, single-marriage women who were cancer free at enrollment in 1982. Breast cancer death rates among women whose husbands smoked were compared with those among women married to men who had never smoked. Cox proportional hazards modeling was used to control for potential risk factors other than ETS exposure. RESULTS: After 12 years of follow-up, 669 cases of fatal breast cancer were observed in the cohort. Overall, we saw no association between exposure to ETS and death from breast cancer (rate ratio [RR] = 1.0; 95% confidence interval [CI] = 0.8-1.2). We did, however, find a small, not statistically significant increased risk of breast cancer mortality among women who were married before age 20 years to smokers (RR = 1. 2; 95% CI = 0.8-1.8). CONCLUSIONS: In contrast to the results of previous studies, this study found no association between exposure to ETS and female breast cancer mortality. The results of our study are particularly compelling because of its prospective design as compared with most earlier studies, the relatively large number of exposed women with breast cancer deaths, and the reporting of exposure by the spouse rather than by proxy."

Response:

It is OEHHA's editorial policy in both this and the previous review to provide a descriptive paraphrase of key points from studies of interest rather than to simply quote authors' abstracts verbatim. OEHHA considers its criticism of the study by Wartenberg et al. to be well-founded. As explained at length in the report and elsewhere in the responses to comments, OEHHA has concluded that the most plausible and parsimonious explanation of the entire body of data on smoking and breast cancer is to infer that there is in fact a causal association between both active and passive smoking and increased risk of breast cancer, relative to the risk for non-smoking females with no lifetime exposure to ETS. This conclusion is coupled with important analyses indicating misclassification of individuals with significant ETS exposure, especially at the critical adolescent and young adult stages, in several non-positive studies. Evidence also suggests a non-linear dose response for breast cancer risk. Taken together these findings

provide an integrative hypothesis which reconciles the reported findings without resorting to extraordinary assumptions of confounding by unspecified factors, or assumptions that proper approaches to control for known covariates failed for unspecified reasons.

Comment 54:

Reynolds *et al*. (2004) conducted a cohort study that used breast cancer incidence as the outcome measure. This study is not included in the Draft Report and should be added to the final report. The authors' description of their study methods and results is as follows:

> "METHODS: In a 1995 baseline survey, 116 544 members of the California Teachers Study (CTS) cohort, with no previous breast cancer diagnosis and living in the state at initial contact, reported their smoking status. From entry into the cohort through 2000, 2005 study participants were newly diagnosed with invasive breast cancer. We estimated hazard ratios (HRs) for breast cancer associated with several active smoking and household passive smoking variables using Cox proportional hazards models. RESULTS: Irrespective of whether we included passive smokers in the reference category, the incidence of breast cancer among current smokers was higher than that among never smokers (HR = 1.32, 95% confidence interval [CI] = 1.10 to 1.57 relative to all never smokers; HR = 1.25, 95% CI = 1.02 to 1.53 relative to only those never smokers who were unexposed to household passive smoking). Among active smokers, breast cancer risks were statistically significantly increased, compared with all never smokers, among women who started smoking at a younger age, who began smoking at least 5 years before their first full-term pregnancy, or who had longer duration or greater intensity of smoking. Current smoking was associated with increased breast cancer risk relative to all nonsmokers in women without a family history of breast cancer but not among women with such a family history. Breast cancer risks among never smokers reporting household passive smoking exposure were not greater than those among never smokers reporting no such exposure."

Response:

Thank you for pointing out this new publication that has become available since the first draft of this document. We have included Reynolds 2004 in our updated draft both in the section on passive smoking, for which they did not find an association with breast cancer, and active smoking, for which they did find an association with breast cancer. OEHHA reviews, interprets, and paraphrases studies rather than excerpting abstracts verbatim. Quotes are used when that is most appropriate and to emphasize exact language of a certain point.

Comment 55:

Five points about this study deserve emphasis:

1. Use of a comparison group that is comprised only of nonsmokers with no ETS exposure reduced the breast cancer risk from HR = 1.32 to HR = 1.25 (marginally significant). This result is opposite the prevailing dogma, based upon speculation by Wells and advanced in the Draft Report, that the long list of null tobacco / breast cancer studies are biased downward by including ETS exposed subjects in the comparison group.

2. Breast cancer risk in never smokers reporting household ETS exposure was not greater than the risk in never smokers reporting no such exposure.

Response:

Of the six published studies that include a comparison within the individual study of active smokers vs. non-smokers and, alternatively, vs non-smokers with no ETS exposure, four found an increase in the risk estimate for the latter compared to the former. The two that did not (including Reynolds), did not in fact determine a full lifetime exposure history for the non-smokers with no ETS exposure. Therefore the observation made in this comment is not relevant. The comparison group in Reynolds et al. (2004) was in fact not non-smokers with no ETS exposure but non-smokers with no residential exposure. Important measures of exposure may have been missed by not including work or other exposure history. Indeed, Reynolds notes that "during the 1980s the workplace replaced the home as the primary source of exposure in this cohort" (Reynolds correspondence JNCI 96 (13) 1042-3, 2004).

Comment 56:

3. The cohort study by Reynolds *et al*. used breast cancer incidence instead of breast cancer mortality as the outcome and the authors report results that are essentially in agreement with the cohort mortality studies by Wartenberg et al. and Egan et al.

4. This study is particularly relevant because it provides information on the ETS / breast cancer risk in a California study group.

5. This null cohort study employs a research design that is not subject to recall bias.

Response:

OEHHA is grateful for these comments on issues in the study by Reynolds et al., which have been taken into account in the study description and analyses that are included in the revised document. It should be noted that the Reynolds study used a control group who were not exposed to ETS in the household. As noted above, Reynolds did not include an analysis of the complete data set that the study had collected to look at other ETS exposures. She does note in her subsequent letter to the editor that "during the 1980s, the workplace replaced the home as the primary source of passive smoking exposures in this cohort"(JNCI 96(13)1042). Reynolds did find an association with active smoking with evidence of positive trends for increasing intensity and duration of smoking. This is important since much of the argument used to refute the many studies that find an association with passive smoking is the inconsistent results from studies of active smoking. While Wartenberg et al. did not examine active smoking, Reynolds is in fact in agreement with the previous study on active smoking from that American Cancer Society cohort (Calle 1994), in finding an association between breast cancer and active smoking.

Comment 57:

The only recent ETS case-control study reviewed in the Draft Report that has employed a research design that could reduce possible recall bias was the study by Delfino *et al*. (2000). That study recruited women after the detection of a suspicious breast mass but before positive diagnosis. Both active smoking status and ETS exposure were determined by questionnaire prior to biopsy diagnosis. Delfino *et al*. did not report a significant breast cancer association with ETS exposure, and no significant risk was observed for active smokers compared with non-ETS exposed non-smokers.

Recall bias is a major concern in breast cancer epidemiological studies because there is a great deal of publicity surrounding every new report of a possible breast cancer risk factor, and a great deal of public awareness and concern about the high prevalence of breast cancer. Recall bias can be controlled by properly designed studies. The studies discussed in the Draft Report that have done the best job of controlling recall bias report no significant association with either active smoking or with ETS exposure.

Response:

Exposure reporting bias in case-control studies comes either from interviewer bias (where study staff interviewing subjects probe more deeply with cases -- not an issue if data were obtained by questionnaire with no interviewer) or recall bias (where cases try harder to remember past

exposure than controls.) With these issues, the concept of "blinding" of the interviewers and subjects to the hypothesis of the study is important. If the main hypothesis under study was a relationship between smoking or smoke exposure and breast cancer, and the interviewers and/or subjects were aware of the hypothesis, then bias might have occurred. At the other extreme, if the smoking hypothesis was not the main purpose of the study and active/passive smoking was among a long list of questions, it is unlikely that bias would have occurred. In response to this and other comments, we have reviewed each case control study individually for potential for bias and included this review in the "Limitations of Studies" section of the breast cancer summary. It is the opinion of OEHHA that the majority of the studies considered adequately addressed potential for bias and studies that did were given more weight in our review . Below are examples of case control studies consideration of bias.

Johnson et al (2000) mailed questionnaires, ergo no interviewer bias. ETS questions among others on breast cancer risk factors. Possible recall or response bias was examined by comparing 71 nonsmoking women with lung cancer and 714 nonsmoking controls in the National Enhanced Cancer Surveillance System. They found an age-adjusted OR of 1.2 (0.7; 7.1) for the association between lung cancer and ≥6 yrs of home ETS. They refer to recent meta-analysis which found an unadjusted risk of 1.2 (1.1;1.4) for lung cancer among lifelong nonsmokers living with a smoking spouse. The authors use the lung cancer results to suggest that bias is likely not seriously affecting the breast cancer risk estimate.

Kropp et al (2002). Self-administered initial questionnaire (so no interviewer bias at this stage) on breast cancer risk factors among which were five questions on active smoking. There was a computer-assisted follow-up telephone interview by interviewers blinded to the subjects' case/control status. There was "no great change in recall for active smoking between the first questionnaire and the follow-up interview even though smoking was only a minor aspect of the initial questionnaire. Taking into account the good quality of the other assessed factors, it seems unlikely that the reporting of active or passive smoking should be greatly biased by case/control status."

Lash & Aschengrau (1999). Structured interviews by trained interviewers covered information on demographics, reproductive events, smoking and medical conditions. This was a

retrospective study so some recall bias may be expected. "However, the substantial associations that were found were within the strata defined by time periods calculated from a series of responses. We do not expect these derived exposures to be susceptible to recall bias." Without knowing more about the study design, it's hard to say if this is true. " Further, neither active nor passive exposure to cigarette smoke has been closely related to breast cancer risk, so recall of exposure should not depend on disease status. However, the widely held perception that smoking cause cancer may contribute to some disease-dependent recall of exposure to tobacco smoke."

Morabia et al. (1996). Data collected from cases and controls under the same conditions by trained interviewers who were not involved in the recruitment and who were blinded to the case/control status. Questions covered the major known or postulated risk factors for BC. Interview was approximately 45 min. of which 20 min were devoted to smoking history. Selection bias was addressed by collecting smoking status on non-participants and indicated there was some "slightly conservative selection bias (that) may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their true smoking status." Questions relating to the subject's attitude regarding passive smoke and smoking in general were compared to their reported exposures. It was postulated that, for similar levels of exposure, if cases were more likely to report having been passively exposed, they would be more likely to report being more preoccupied by passive smoke in their everyday lives than were controls. The data did not support this so the authors suggest recall bias was minimal. As with Lash and Aschengrau, the authors suggest that passive smoking is not associated with breast cancer in the public's mind, thus minimizing disease-dependent recall bias. They calculated that even if due to erroneous recall, 15% of the unexposed cases and 0% of the unexposed controls had been misclassified as passive smokers, the unbiased crude OR for eve-passive smoking would still be significant (1.8, 1.2;2.8).

Sandler et al. (1985). Mailed questionnaires – no interviewer bias. However, the focus of the study appeared to be smoking. Interview of 649 relatives of subjects showed good agreement between subjects' and relatives' responses regardless of case/control status, suggesting minimal

recall bias. Also, the hypothesis that parental smoking may cause cancer was not widely known at the time.

OEHHA has consistently considered the possible influence of recall bias and other sources of misclassification on the findings of studies reviewed in the document. While it is difficult to demonstrate conclusively that such effects have been eliminated in any questionnaire-based study, careful design and administration of the questionnaire or other data collection operations can address the likelihood of major impacts. In the case of the study by Delfino et al. (2000), OEHHA noted in the summary provided in the document that

> "Smoking status, active and passive, was collected via questionnaire prior to biopsy diagnosis."

This procedure might reasonably be expected to minimize recall bias assuming that the above conditions were met and that there was no general publicity about a potential link between the disease and exposure of interest. OEHHA disagrees with the commentator's concern, expressed here and elsewhere, that recall bias is so overwhelming a problem as to negate the positive findings in many studies.

Comment 58:

There is currently no molecular or animal model that explains the mechanism underlying breast cancer susceptibility. Current molecular epidemiology studies are just beginning to explore the genetic level of individual risk and do not explain individual susceptibility.

Response:

While it would be inappropriate to suggest that all the features of individual sensitivity can be explained by current knowledge, some underlying principles have been identified. There are various epidemiological and biochemical studies (for instance, publications cited in the document by Morabia et al.) which explore the relationship between an individual's genetic make-up governing biochemical characteristics and incidence of ETS-induced cancer. These generally relate to the metabolism and activation of the various genotoxic carcinogens which, as OEHHA points out in the report, are abundant in both ETS and directly inhaled tobacco smoke. Other investigators have evaluated the mutational spectra of breast tumors. Conway et al.

(2002) demonstrated that cigarette smoking influences the prevalence and spectrum of p53 mutations in breast tumors. Breast tumors from ever-smokers were more likely to have p53 mutations involving G:C to T:A transversions than non-smokers; current smokers have statistically higher levels of these p53 mutations than non-smokers. These p53 mutations are consistent with exposures to PAHs and nitrosamines which are found in tobacco smoke.

Comment 59.

SECTION VII: Heart Disease.

The Draft Report states that a growing body of evidence supports the conclusion reached in the 1997 OEHHA report that ETS exposure increases the risk of cardiovascular disease by about 20-50%. The Draft Report claims to have reviewed eight "newer" epidemiological studies. This claim is misleading because included in that number are three highly selective meta-analyses (by He et al. 1999, Law et al. 1997, and Wells 1998) which offer no new data and selectively reject null results from published studies. Such exercises are result-driven and do not conform even to basic standards of meta-analysis. In addition, even if these reviewers had pooled all of the relevant ETS / CHD data that would not address the fundamental problem with the meta-analysis method when it is applied to the ETS / CHD issue. Meta-analysis cannot correct underlying flaws in the spousal smoking definition of ETS exposure, it simply insures that lifestyle and other SES-related factors introduced by the design will reach statistical significance. Neither the newer original epidemiological studies nor the meta-analyses cited in the report address the significant methodology problems that undermine the report's conclusions.

The meta-analysis by He *et al*. was sharply criticized in a *New England Journal of Medicine* editorial by Bailar (1999), as well as in several letters to the *NEJM* editor. The criticisms are directed not only at the review by He *et al.*, they also touch upon many of the ETS / CHD methodological problems discussed below. The Draft Report ignores the following highly critical discussion:

The Draft Report repeats claims made in the 1997 report that clinical and animal laboratory studies add to the biological plausibility of an ETS / CHD risk. The studies cited in the report can not explain how an ETS / CHD risk could be nearly equal to the risk typically attributed to active smoking (about 30% and 70%, respectively), since environmental tobacco smoke exposure is two to three orders of magnitude lower than exposure due to active smoking.

Response:

The reasons for this apparent relationship are not entirely clear and are likely multifactorial. However, the plausibility concerns derive, in part, from the erroneous assumption that ETS is essentially diluted mainstream smoke. There are significant differences in the chemical composition of ETS and mainstream smoke, some of which are germane to CHD such as higher

levels of CO and nicotine in ETS. In addition, possible differences in the induction of enzyme systems in persons passively vs actively exposed to smoke, and individual sensitivities to smoke components likely all contribute. As suggested by Law and Wald (2003) the response of ischemic heart disease to smoke exposure appears to be non-linear with a strong response at low smoke levels that tends to plateau at higher levels. Part of this effect may be related to the concentration differences between ETS and mainstream smoke that result in different exposures of passive and active smokers. The more concentrated mainstream smoke fosters the formation of larger aggregates from the particulate phase that more rapidly deposit in the upper airways of the smoker. By comparison, the particulates in the more dilute ETS are more dispersed and so tend not to aggregate. These smaller particles are better able to penetrate deeper into the lungs where they and the compounds adhering to them are more readily absorbed into the circulatory system.

In addition, recent in vitro studies of the responses of fibroblasts exposed to solutions containing whole sidestream or whole mainstream smoke found a sidestream smoke-specific effect (Wong et al., 2004). Fibroblasts were exposed for four hours to media containing sidestream smoke at nicotine concentrations (~2 µg/ml) adjusted to reflect typical tissue nicotine levels in nonsmokers following 78 minutes of exposure to ETS in a smoky room, or to a similar preparation of mainstream smoke. Cells were examined microscopically following staining with DIOC6, a stain used to label the endoplasmic reticulum (ER). In control cells not exposed, the ER was well developed, concentrated around the nucleus but spread throughout the cytosol. By comparison, the ER in cells in sidestream smoke-containing media showed punctated staining reflecting fragmentation and coalescence of the ER around the nucleus, whereas the ER in cells exposed to the mainstream smoke solution looked more like that of the control cells. Similarly, sidestream smoke had a differential negative effect on the integrity of Golgi vesicles and the distribution of the chemokine cIL-8 compared to control and mainstream smoke-exposed cells.

Experiments such as these indicate that cellular responses to ETS are qualitatively different from those to mainstream smoke and that questions of biological plausibility must take into account differences in mechanisms of action. In addition, it is now well accepted that some of the effects

(on endothelium and platelets, for example) manifest at low exposure levels (Glantz and Parmley, 1995; Law and Wald, 2003; Schmid et al., 1996; Celermajer et al., 1996).

Comment 60:

The studies that are cited in the report fail to establish two critical connections—they do not establish that the endpoints they measure actually increase CHD risk, and they do not establish that the endpoints they measure are unique to ETS exposure and are not elicited by similar common exposures (e.g. exhaust from internal combustion engines).

Response:

The connections between the measured endpoints, such as loss of arterial flexibility, increased intima-media thickness, increased aortic lesion area, decreased endothelial responsiveness and lower HDL-C levels observed in ETS-exposed human subjects, have all been associated with increased CHD risk in other studies. If these effects are also elicited by other exposures, that may indicate a need to consider possible additive effects of common exposures but does not reduce the importance of exposure to ETS.

Comment 61:

As discussed below, none of the key problems that undermined the conclusions of the 1997 report have been adequately addressed in the epidemiological studies or in the Draft Report. The data still do not provide convincing evidence even of an association between ETS exposure and CHD, let alone support a causal inference.

This section of the Draft Report suffers from another related problem—it treats all of the studies cited as if they contributed comparable data and used comparable methods. This is obviously not the case, and leads to confusion. The meta-analyses should not be listed in the same table and reviewed in the same section as the original epidemiological studies. The same thing is true of the animal and clinical laboratory studies. Both types of studies should be tabled and reviewed separately so that the reader can more easily find and compare the results of the epidemiological studies. In addition, the epidemiological studies should be grouped by heart disease outcome so that it is clear that two of the five newer studies relate to CVD (in this case stroke) and not to CHD, which was the topic of the 1997 report.

Response:

The table and the text group meta-analyses at the beginning of the section, followed by original epidemiological studies, and then clinical laboratory studies. This grouping and the explicit

labeling of meta-analyses as such in the study description column in the table should facilitate the comparisons among studies of each type by the reader.

Comment 62:

The animal and clinical laboratory studies provide data on physical and chemical responses to tobacco smoke. The exposures involved in many of the studies are not true ETS at realistic environmental exposure levels and are of limited value in determining what, if any, significance actual ETS exposure might have on the same end points. An important related question is whether or not the reported chemical or physical responses are unique to ETS exposure in the first place. The studies do not demonstrate that this is the case. Studies are needed that repeat the same end point measurements after subjects are exposed to a variety of related substances that are routinely encountered in the environment. Such exposures as automobile and diesel exhaust emissions, exposure to gasoline fumes when pumping gas, exposure to PAH's released when burning gas and oil for home cooking and heating, and exposure to smoke from wood-burning fires are some examples of related exposures. If everyday exposures such as these elicit responses similar to those reported in ETS exposure studies then it would be virtually impossible to isolate an ETS component of any associated health effect, even if one existed. At this time, the animal and clinical laboratory studies are of very limited value in understanding the implausibly high reported spousal smoking / CHD association.

Response:

Unquestionably environmental exposures other than ETS may contribute to these various endpoints and confound the results of specific studies. However, the associations with ETS appear in numerous studies representing diverse combinations of population, location, and confounder control, which lend support to the association with ETS. Moreover, the comment does not provide specific citations of evidence to support the hypothesis that these theoretical problems are a) real, and b) capable of explaining the effects associated with ETS exposure.

Comment 63:

Most of the epidemiological studies reviewed in the 1997 report found that ETS exposure had a positive but not statistically significant association with CHD. This continues to be true of newer studies. In the current Draft Report only the studies by Bonita *et al*. (1999) and You *et al*. (1999) report any statistically significant associations. Both studies have severe limitations, as noted in the Draft Report. The Bonita study has only broad questionnaire data on spousal smoking exposure and no data on ETS exposure duration or intensity. The study did not distinguish between fatal and non-fatal stroke, different types of stroke, or between more or less severe stroke. The study did not control for possible confounding by diet or many other known stroke risk factors. The study did not properly adjust for age differences between cases and controls, and it did not use uniform methods to collect data from cases and controls.

Response:

Contrary to this comment's assertion, the studies by Rosenlund et al. (2001) and Ciruzzi et al (1998) also reported statistically significant associations between CHD and ETS exposure. OEHHA acknowledges that the Bonita et al. study has a number of the limitations mentioned in the comment. However, we view the inclusion of all strokes irrespective of type and severity as a strength, not a weakness. It is because of these limitations that OEHHA concluded that the data are suggestive, rather than conclusive, regarding a causal association between ETS exposure and stroke.

Comment 64:

Essentially the same design flaws apply to the spousal smoking / stroke study by You *et al.* (1999). That study did collect limited spousal smoking exposure data (only two exposure groups), but only when the authors combined smokers and non-smokers did they report a significant spousal smoking / stroke association. Given the concerns about selection bias and poor age adjustment in this study, speculation in the Draft Report about the meaning of the pooled (active + spousal smoking) association is not convincing. It is highly unlikely that active smokers would exhibit any effect of spousal ETS exposure given their vastly higher levels of exposure to tobacco smoke, both from their active smoking and exposure to their own ETS. The most likely explanation of these results is confounding by shared lifestyle-related exposures. Smokers who are also married to smokers have the least healthy lifestyles and the most competing risk factors for stroke.

Response:

While this study suggested an association between ETS and ischemic stroke, it was in consideration of these concerns that the authors indicated (and OEHHA noted in its summary) their work should be viewed as hypothesis generating rather than definitive.

Comment 65:

The ETS / MI epidemiological study by Rosenlund *et al*. (2001) used an active smoking definition that could have included someone who smoked for less than one year, or who smoked intermittently, in the control group. The same thing is true of the light and intermittent smokers misclassified as non-smokers in the spousal smoking exposure group. In fact, most ETS studies rely only on answers to historical smoking questions obtained by questionnaire and interview. Light and intermittent smokers are the most likely to be misclassified as non-smokers. Substantial active smoking misclassification is likely in all of the ETS studies.

Response:

As noted in our update, inclusion of smokers in the control group would tend to diminish any apparent effects due to ETS and make the OR estimates artificially low. On the other hand, inclusion of intermittent smokers in the ETS-exposed group could artificially inflate risk estimates. Population-based validation studies suggest about a 1.2% misclassification of ever-smokers as never-smokers in case-control studies such as this one (Nyberg et al., 1998). Misclassification at this level would not be expected to substantially affect the results reported by Rosenlund et al. However, the point regarding exposure misclassification is well taken and underscores the need for independent, preferably biochemical, verification of smoke exposure.

Comment 66:

In the Rosenlund study data were collected by postal questionnaire and interview. Although exposure to several heart disease risk factors were included on the questionnaire, they did not have any effect on the primary analysis. This may be explained by the failure to measure anything meaningful with these questions in the first place. Questions about age, gender, height, weight, hypertension, and diabetes can be expected to produce reasonably valid data. On the other hand, questions about SES, dietary intake of fat and fiber, blood lipid levels, and job strain can not be expected to elicit valid data on these variables. The reason statistical adjustment for these factors did not have any effect on the spousal smoking / CHD analysis is most likely due to failure of the questionnaire to provide valid data in the first place. This leaves uncontrolled confounding as a possible explanation for the statistically non-significant associations reported in the study.

Response:

The inclusion of independent verification of biochemical and psycho-social parameters would certainly have improved our confidence in Rosenlund's results by limiting bias and reporting errors. However, from the methodology reported by Rosenlund et al. for collecting dietary and SES data, we have no reason to suspect that the data are not reasonably valid nor that uncontrolled confounding is a likely explanation of the results.

Comment 67:

The Draft Report once again repeats inaccurate descriptions of the studies by LeVois and Layard (1995), and Layard (1995), and cites references that they claim support their criticisms. We provided detailed responses to these distortions and misrepresentations in our comments on the OEHHA 1997 report. Our comments and corrections of errors were never acknowledged and

addressed by the earlier report, and it is not surprising that they were ignored in the current draft. It appears that the authors have not read the papers in question or our comments. For that reason, I repeat our detailed response below.

It is incorrect to claim that recent ETS/CHD data support the claim that ETS increases the risk of heart disease. The CPS-I, CPS-II, and NMFS data reported by LeVois and Layard (1995), and Layard (1995) clearly do not support such a claim. It is incorrect and misleading to claim that the report by Steenland et al. on CPS-II data provides any more support for an ETS/CHD association than the CPS-II portion of the paper by LeVois and Layard.

Both the current Draft Report and the 1997 report criticize the CPS-II analysis reported by LeVois and Layard (1995), and instead rely exclusively on the ETS/CHD report by Steenland et al. (1996), and the accompanying editorial by Glantz and Parmley. Those reports and the OEHHA draft mischaracterize our paper, which presents an analysis and interpretation of all of the ETS/CHD epidemiologic data available at the time of publication. We believe that both groups of authors draw conclusions that are not supported by a review of all of the data presently available.

First, it should be emphasized that our conclusions regarding both the existence of publication bias in the ETS/CHD epidemiologic literature, and the lack of association between CHD and ETS exposure were based not just on CPS-II, but also on our analysis of data from CPS-I and the National Mortality Followback Survey (NMFS) (Table 1), as well as results from the previously published ETS/CHD epidemiologic studies. In our analysis of the CPS-I study we found no association between spousal smoking (whether defined as ex-, current-, or any-smoking) and death from CHD, either in never smoking males or females, and no sign of a dose-response in either group. We also observed no ETS/CHD association, and no sign of a dose-response, in the NMFS data.

Table 1
CPS-I Spousal Smoking and CHD Death[1]

Men -- 7758 CHD deaths* among never smokers.

Spousal Smoking	rr	95% CI
Ex	0.95	(0.83-1.09)
current:		
1-19	0.99	(0.89-1.09)
20-39	0.98	(0.85-1.13)
40+	0.72	(0.41-1.28)
Any	0.97	(0.90-1.05)

Women -- 7133 CHD deaths* among never smokers.

Spousal Smoking	rr	95% CI
Ex	0.99	(0.93-1.05)
current:		
1-19	1.04	(0.97-1.12)
20-39	1.06	(0.98-1.15)
40+	0.95	(0.78-1.15)
P/cigar	1.06	(0.99-1.14)
Any	1.03	(0.98-1.08)

National Mortality Followback Survey
CHD/ETS Case-Control Study[2]

Men

Spousal smoking	Cases	Controls	rr	95% CI
No	378	783	1.0	
Yes	97	215	0.97	(0.73-1.28)

Women

Spousal smoking	Cases	Controls	rr	95% CI
No	459	969	1.0	
Yes	455	961	0.99	(0.84-1.16)

[1] LeVois and Layard (1995) [2] Layard (1995)
[*] Layard (1995b)

Response:

We would like to state that comments made by this reviewer on the 1997 report were in fact reviewed, considered, and responded to in 1997.

Whether the control populations in the NMFS and CPS-I studies were truly not exposed to ETS is a serious concern given the prevalence of smoking and the ubiquity of ETS in the home, work and social environments at the time of those studies. Regarding the exposed group, there are other concerns with these and other studies that rely exclusively on marriage to a smoker as the definition of ETS-exposed. If the smoking spouse is actually an ex-smoker or rarely smokes in the presence of the individual identified as ETS-exposed, then the latter's exposure may be more similar to that of the control group. Conversely, a person married to a non-smoker may have worked with a smoker, a common occurrence in previous years; thus, this person if counted as a control subject would actually have been ETS-exposed. Thus the actual ETS exposures of the control and exposed populations in the older studies may be so similar that any ETS exposure effects are lost. Indeed, the American Cancer Society repeatedly communicated with the authors that CPS-I was not informative with respect to ETS exposure due to deficiencies in the collected data (Thun, 2003). The NMFS was further hampered by reliance on proxy data from next of kin with its attendant biases. For these reasons we have tried to emphasize studies that address these issues.

Limitations of the case-control study by Layard (1995), which uses data from the 1986 NMFS cohort, include reliance exclusively on information provided by next-of-kin of subjects who had died, and failure to specify causes of death for control subjects beyond indicating the excluded causes of death, raising concerns regarding misclassification bias of ETS exposure and selection bias of controls. Among other problems with the Layard (1995) study are the apparent lack of matching for age at death or race: cases were older (mean age at death: men, 72.6; women, 78.2) than controls (64.8, men; 71.9, women), and a higher percentage of cases (74.9%, men; 73.9% women) than controls (68.2%, men; 68.4%, women) were white.

Comment 68:

Steenland et al. restrict attention only to the CPS-II data, never mentioning CPS-I despite the fact that in CPS-I there are nearly five times as many CHD deaths among never smokers as there are in CPS-II. Neither the CPS-I results, nor the NMFS results are mentioned in their list of ETS/CHD epidemiologic studies presently available. This omission has the effect of biasing ETS/CHD meta-analysis. All of the published data together do not support the conclusion that ETS increases the risk of heart disease.

Response:

In our view, Steenland et al. were justified in excluding the CPS-I and NMFS data for the reasons given in the previous response. CPS-I was not designed to study the effects of passive exposure and inclusion of CPS-I data could bias the analysis due to the inability to define a truly non-exposed group (Thun, 2003).

Comment 69:

Despite differences in selection criteria that led Steenland et al. to exclude from consideration over 20,000 subjects that we thought should be included in their largest CPS-II subcohort (their Table 2), and Steenland, et al.'s inclusion of an additional year of follow-up data not available to us, the results of their analysis of CPS-II data are essentially in agreement with ours, as shown below (Table 2).

Both sets of analyses in Table 2 report that there is a significant ETS/CHD association in CPS-II males living with a current smoker at the start of the study, due mainly to a risk elevation in men who report the lowest levels of ETS exposure. There is a strong negative dose-response among never-smoking men who were married to a current smoker at baseline, which is inconsistent with a true ETS effect. There is not a significant association between ETS exposure and CHD death in CPS-II women never-smokers, nor is there any sign of a dose-response.

The lack of support for an ETS/CHD association in CPS-II females is particularly important for two reasons. First, there are more than two times as many CHD deaths among never-smoking females as there are among never-smoking males in the CPS-II data, making the female data especially important to any interpretation of the CPS-II data. Second, the great majority of published data from other epidemiologic studies on the association of ETS and CHD are for females, making the CPS-II female data particularly relevant to any meta-analysis and interpretation of the pooled ETS/CHD epidemiologic data.

Table 2: Comparison of CPS-II Results
Reported by Steenland et al., and LeVois & Layard

Sex	Cigarettes/day Spousal Smoking	Steenland et al	LeVois and Layard
Men	Ex	0.96 (0.83-1.11)	0.81 (0.70-0.95)
	1-19 current	1.33 (1.09-1.61)	1.36 (1.10-1.68)
	20 current	1.17 (0.92-1.48)	
	21-39 current		1.26 (1.00-1.58)
	20+ current	1.09 (0.77-1.53)	
	40+ current		1.13 (0.61-2.11)
	Any		0.97 (0.87-1.08)
Women	Ex	1.00 (0.88-1.13)	0.99 (0.86-1.13)
	1-19 current	1.15 (0.90-1.48)	1.14 (0.86-1.51)
	20 current	1.07 (0.83-1.40)	
	21-39 current	0.99 (0.67-1.47)	

20-39 current		0.98 (0.75-1.29)
40+ current	1.04 (0.67-1.61)	1.27 (0.80-2.01)
Pipe/cigars only		0.98 (0.79-1.20)
Any		1.00 (0.88-1.14)

Steenland et al. are inconsistent in the choice of ETS exposure definitions in their calculation of CHD risk. On the one hand they argue that attention should be restricted to CPS-II cohort members who were married to a current-smoker at base line when looking for an ETS/CHD association. On the other hand, the dose-response data that Steenland et al. report in the analyses presented in their Table 3 includes data for subjects married to ex-smokers at baseline. These are the same ever-smoker data they speculate may have biased our analysis.

Steenland et al. may prefer ever-smoker trend data over the current-smoker data they argue in favor of elsewhere because the ever-smoker data show some sign of a positive trend in CHD risk with exposure. However, CPS-II subjects married to ex-smokers at base line tend to have less total years of exposure and are, therefore, at the low end of the exposure distribution. This produces an apparent positive trend in CHD risk with increasing exposure which is due mainly to a risk deficit in subjects married to ex-smokers, not to an increase in risk with increasing exposure to current smokers. Since the observed CHD risk deficit is inconsistent with any causal ETS/CHD hypothesis, an implausible risk deficit among subjects married to ex-smokers has produced a positively biased estimate of trend in CHD risk reported by Steenland et al. in their Table 3.

In our analysis of the CPS-II data we chose exclusion, exposure, and confounder definitions that preserved as much of the relevant data as possible, and were as consistent as possible with the definitions used by others. Our exclusion criteria, and the effects of these exclusions are summarized in Table 3. Exposure was defined as either married to an ex-smoker at baseline, or as the current cigarettes per day smoked by the spouse at baseline. Potential confounders initially considered were age, race, indices for weight and exercise, highest level of education, dietary factors, alcohol consumption, history of hypertension, and history of diabetes. Only age and race were retained for our final analyses, as the other potential confounders had no appreciable effect on any of the reported associations.

Table 3
CPS-II Females (N=676,612)*

Numbers of women excluded from analysis:

Not married or spouse not in study	227,856
Not never smoker	209,589
Spouse smoking information missing	12,736
Death date unknown	364
Total exclusions	450,545
Used in analysis	226,067

* Total in CPS-II female database; Layard 1995b

We reported relative risks both for never-smokers married to ex-smokers, and for never-smokers married to current-smokers, categorized by packs per day at baseline.

Restriction of attention to never smokers married to current smokers at the start of follow-up discards relevant information. To be consistent with a causal hypothesis, ex-smoker data would be expected to produce some positive CHD risk. Many ETS/CHD studies and meta-analyses have retained the ex-smoker data for their final ever-smoker spouse exposure definition.

There is considerably more variation in spousal smoking exposure definitions used in previous ETS/CHD studies than suggested by either Steenland et al., or by Glantz and Parmley. Of the 14 studies mentioned by Steenland et al., seven are cohort studies, and seven are case-control studies. Two cohort studies (Butler, 1988, and Garland, et al. 1985) reported results for both ex- and current-smoking spouses at baseline. Glantz and Parmley (1991) used the ever-smoker relative risks for Garland and Hirayama (1984) in their meta-analysis, but used the current smoker relative risk for

Butler. Hole and Gillis (1989) reported results only for exposure to ever-smokers at baseline. Humble, et al. (1990) and Svendsen, et al. (1987) reported results only for current-smokers at baseline. Hirayama reported results for two groups -- the first comprised of ex-smoking spouses together with current smokers of 1-19 cigarettes per day, the second comprised of current smokers of 20+ cigarettes per day. Glantz and Parmley combined these two groups into an ever-smoker relative risk for their meta-analysis. Helsing, et al. (1988) reported results by exposure score categories that largely divided cohabitants into ex- and current-smokers at baseline, but Glantz and Parmley used the ever-smoker relative risk in their meta-analysis. In none of the seven cohort studies was there any account taken of smoking cessation over the course of follow-up, which ranged from 6 to 20 years.

Of the seven case-control studies, two (Martin, 1986; and LaVecchia, 1993) reported results for ex- and current smoking spouses. Four (two by He, et al. (1989, 1994); Lee, et al. 1986; and Muscat, 1995) reported results for ever-smoking spouses. Jackson, (1989) reported results for current smokers, and Dobson (1991) may have done so as well, although the report by Dobson is not clear on this point.

Response:

Steenland et al.'s (1996) analyses of the CPS-II cohort differed methodologically from those of LeVois and Layard (1995), and Steenland et al. (1996) did report statistically significant results. The study by Steenland et al. (1996) presents results from four analyses of the CPS-II cohort, three of which dealt specifically with ETS exposure from spouses; the fourth analysis investigated the effects of ETS exposure at home, at work, and in other settings. The first analysis was conducted only among those married individuals with spouses also enrolled in the CPS-II study, and for whom there were valid dates of marriage and sufficient data on smoking cessation to indicate whether the spouses had smoked during marriage. The second, third and fourth analyses utilized specified subsets of eligible subjects derived from the first analysis. Small increased risks for CHD mortality in men and women in association with current exposure to spouses' smoking were found in each of the analyses, with statistically significant results only in nonsmoking men. There was, however, no association between risk of CHD mortality in nonsmoking men and women and being married to spouses who were former smokers. The fourth analysis found small elevated risks associated with all sources of ETS exposure, although only the association between CHD risk in nonsmoking men and ETS exposure at home was statistically significant.

The differences in Steenland et al.'s (1996) findings and those reported by LeVois and Layard (1995) are noteworthy given that both analyses utilized data from the CPS II study. The size of the relevant study population and the number of CHD deaths included by Steenland et al. (1996) differed from those included by LeVois and Layard (1995). In contrast to the detailed description of the inclusion and exclusion criteria presented by Steenland et al. (1996), LeVois and Layard (1995) provided few details regarding their study methods. Differences in the follow-up period, in the definition of spousal smoking or other criteria for inclusion and exclusion may have contributed to the differences in these two reports. Exclusion of former smokers is not arbitrary but reflects an understanding of the literature on tobacco smoke and CHD; a rapid reduction in heart disease risk is seen among active smokers upon cessation of smoking, and a similar effect of cessation of exposure to ETS probably occurs.

Comment 70:

Inconsistencies in the ETS exposure definition described above do not support the claim that marriage to a current smoker is the preferred exposure definition in previously published ETS/CHD studies, nor the claim that our use of an ever-smoker exposure definition could explain our failure to find an ETS/CHD association.

Despite differences in composition of both exposed and comparison groups, a global ever-smoking spouse exposure index has been most often used to calculate summary relative risks by previous reviewers. There is very little evidence that the distinction between ever-smoking and current-smoking spousal exposure definitions has made much difference.

Response:

It has not been well appreciated in many studies that ETS appears to have both acute and long-term effects that may differentially affect the CHD risk in different individuals. For example, individuals with compromised cardiovascular function maybe more likely to experience a CHD event in response to the acute effects of ETS exposure, such as platelet aggregation, decreased oxygen delivery to heart muscle, and decreased arterial responsiveness compared to otherwise healthy individuals. Use of the current-smoking definition would likely be more relevant to the detection of risk in this group. As a result, the exposure definition used (ever-smoking or current smoking) could selectively favor detection of CHD risk in certain subpopulations but not others. However, until the susceptibilities of individuals in the study populations can be more thoroughly characterized, analyses that use both exposure definitions are more likely to reveal any

associations between ETS exposure and CHD. The effect of reducing CHD risk following cessation of smoking likely is relevant to passive smoking. That CHD risk may diminish following cessation of exposure to ETS was suggested by the prospective study of Whincup et al. (2004) in which the relatively strong association of CHD risk with baseline serum cotinine levels during the first 5-10 years of follow-up attenuated with longer follow-up periods. During this time, active smoking, and thus ETS exposure, declined markedly in Britain, the site of the study. These considerations argue for evaluating CHD risk in spouses of current smokers separately from spouses of former smokers.

Comment 71:

More to the point, the data presented in Tables 4 and 5 below show that there is little support for the proposition that CHD risk declines rapidly with smoking cessation to be found in the CPS-II data, undermining the argument that CPS-II analyses should be restricted only to subjects married to current smokers at baseline.

We have recently calculated CHD relative risks for never-smokers married to ex-smoking spouses categorized by years since they had quit smoking at study entry (Table 4):

Table 4

CHD Relative Risks for Never-Smokers
Married to Ex-Smoking Spouses in CPS-II
Categorized by Years Since Quit Smoking at Baseline

	Years Quit Smoking			
	0-2	2-5	5-10	10+
CPS-II				
Men (N=103,388)	0.78	0.92	0.66	0.83
Women (N=222,932)	1.12	1.15	1.18	0.92

In addition, the 1990 Surgeon General's report cited by both Steenland et al., and by Glantz and Parmley, presents the following data (Table 5) from CPS-II on the decline in CHD risk for ex-smokers after they quit smoking:

Table 5
Decline in CHD Risk in CPS-II Ex-Smokers
Categorized by Years Since Quit at Baseline*

	Current smokers	Ex-smokers Years since quit			
Men		< 1 year	1-2	3-5	6-10
<21 cigs/day	1.93	1.43	1.61	1.49	1.28
21+ cigs/day	2.02	2.56	1.57	1.41	1.63
Women					
<20 cigs/day	1.76	2.13	0.87	1.31	0.74
20+ cigs/day	2.27	1.41	1.16	0.96	1.88

1990 Surgeon General's report

In Table 4 there is no evidence of a decline in CHD risk for either male or female CPS-II never smokers exposed to spouses who had quit smoking at study baseline. Table 5 shows only a modest decline in risk with years quit, within the first ten years, among CPS-II ex-smokers themselves. Clearly, the CPS-II data do not support claims by Glantz and Parmley that CHD risk in active smokers essentially disappears in five years, and that defining spousal smoking exposure as marriage to an ever-smoker strongly biased our CPS-II analysis toward the null.

Response:

How much the CHD risk from active smoking diminishes in five years is perhaps an open question. However, an analysis of AMI risk following cessation of active smoking by Lightwood and Glantz (1997) found risks approaching unity after five years. This may or may not have direct bearing on the attenuation of CHD risk with cessation of ETS exposure. In the context of CHD risk with ETS exposure, studies by Rosenlund et al. (2001), Raitakari et al. (1999) and Steenland et al. (1996) all reported an attenuation of risk following exposure cessation. For example, Rosenlund et al (2001) reported that the risk of myocardial infarction associated with ETS dropped from 1.39 (95% CI 0.91; 2.10) after less than one year following cessation of ETS exposure, to 1.30 (95% CI 0.85; 1.98) for 1-6 years cessation, 1.11 (95% CI 0.70; 1.74) at 7-16

years post-exposure, and 0.92 (95% CI 0.58; 1.44) after 16 years. In this example, there is no excess risk for CHD among individuals exposed to spousal smoking 16 years previously but not since. Inclusion of such individuals in the ETS-exposed group would dilute the measured effect and bias towards the null. Any assessment of potential recovery following cessation of ETS exposure must take into account the increase in CHD risk associated with increasing age.

Comment 72:

It is also clearly inconsistent for Glantz and Parmley, in their editorial, to stress the superiority of using marriage to a current smoker as the exposure definition, and to criticize the NMFS study by Layard (1995) both for using ever-married to a smoking spouse as the exposure definition, and death certificates for the CHD outcome. Glantz has expressed his approval of the study by Helsing, et al. (1988), and has used that study's ever-smoker spouse data for meta-analysis purposes. Death certificates also were used for the CHD outcome in the Helsing study (as they were in most other ETS/CHD cohort studies). Yet Glantz and Parmley criticize Layard for using the same ever-smoker and death certificate based data in the NMFS case-control study.

In fact, a strength of the case-control study by Layard is that it uses data on spousal smoking habits that were collected close to the time of death, ensuring that current smokers in the NMFS study actually continued to smoke up until the time of death of the CHD case. In contrast, in Helsing et al., and all other cohort studies, "current" spousal smoking data were only collected at baseline, typically years prior to death, with no accounting for changes in spousal smoking habits.

Response:

The studies by Helsing et al (1988) and Layard (1995) are difficult to compare since the former was a prospective study, and the latter a retrospective study. Glantz and Parmley's criticisms of Layard appear not to be of the use of death certificate data per se, but rather of the use of marriage to an ever-smoker. It is true that the Helsing study collected spousal exposure information only at baseline and as a result did not reflect any subsequent changes in spousal smoking. However, the certainty of the smoking ascertainment at baseline in a prospective study such as Helsing's is higher than for any time in a retrospective study such as Layard's. The dependence of the Layard's NMFS study on next-of-kin for smoke exposure information makes recall bias and exposure misclassification a significant concern, especially since the next-of-kin in the NMFS may not have lived in the same household.

Comment 73:

In addition to inconsistencies in their use of data restrictions, and the poor support for those restrictions found in the CPS-II data, other questions are raised by the ways in which Steenland et al. restrict their analysis. It would have been more informative if the authors had indicated what effect specific restriction criteria had on their selection of subjects, and on the ETS/CHD associations they report. For instance, there is no way to tell which exclusion criteria resulted in the loss of 40%-50% of the CHD deaths among never-smokers in the analyses reported in their Table 3.

Response:

It is not clear to what the commentator is referring by "inconsistencies in their use of data restrictions…" With respect to Table 3, the reduction in CHD deaths is roughly proportional to the reduction in the size of the subcohort based on the exclusion criteria of single marriage.

Comment 74:

In the analyses reported in Table 5, Steenland et al. look only at concordant exposure data, the subset possibly subject to the least exposure misclassification according to the authors. Unfortunately, only about one half the CPS-II subjects provide both self reported ETS exposure data and concordant data from the spouse. We question whether these are really more reliable ETS exposure data. Most of the lost data resulted from the fact that about 40% of all subjects left the self-reported home ETS exposure questions blank. Data from those subjects were excluded by Steenland et al. from their concordant data analyses. It is likely that a substantial portion of the blank responses to the home ETS exposure question are meant to mean zero ETS exposure. If that is the case, then the data used for these analyses clearly do not reflect true CPS-II ETS exposure rates. The fact that so much data is lost also increases the possibility that the remaining subjects may be a biased subset of the CPS-II data.

Response:

Steenland's analysis of concordant pairs was just one of several analyses they performed of the CPS-II data. It is telling that the analysis that arguably entails the least exposure misclassification, at least as regards household exposure, also generates the highest excess risk estimates (men 23%; women 19%). How representative a sample is of the whole population is always an open question. However, in the absence of response data, it is merely speculation to assert that the missing responses represent zero ETS exposure and that, as a result, the remaining subjects represent a biased subset. Restricting the analysis to the subset with the best defined ETS exposure strengthens conclusions regarding the ETS/CHD association.

Comment 75:

A related question concerns the calculation by Steenland, et al. of pack-years of exposure used in many of their analyses. This calculation was apparently based upon assumptions not mentioned in their report. The CPS-II questionnaire does not contain a detailed smoking history section. There is no way of accounting for changes in smoking behavior. Any calculation of pack-years from these data, therefore, is based upon speculative assumptions. For this reason, in our analyses we defined exposure exactly as reported -- either as marriage to an ex-smoker at baseline, or in cigarettes per day smoked by current smokers at baseline.

Response:

Steenland et al. noted that current smokers were asked about the age of smoking initiation, amount of smoking per day, and the total number of years of smoking for each tobacco type. It should be possible to calculate pack-years from these data.

Comment 76:

It is quite surprising that Glantz and Parmley should use the long overdue publication of part of the relevant ACS data on ETS and heart disease to support their argument that publication bias has not influenced the ETS/CHD epidemiologic data. The Steenland, et al. report is only a partial, and inadequate, response to our paper on publication bias. It ignores completely our analysis and publication of results for the much larger number of relevant CHD deaths in CPS-I, as well as publication of the NMFS study. We stand by our conclusion that publication bias is a dominant factor in the epidemiologic literature on ETS and heart disease.

Response:

Inasmuch as CPS-I and NMFS have control groups with questionable ETS exposure and, as mentioned above for NMFS, uncertainties about the degree of spousal smoking, the exclusion of these studies is appropriate and not necessarily evidence of publication bias.

Comment 77:

Finally, comments by Steenland et al. and by Glantz and Parmley that workplace exposure to ETS is likely to be a cause of heart disease is simply speculation. This conclusion does not follow from the data presented, which show workplace relative risks that are not significant, and are very near 1.0 in all categories. This null result is consistent with most of the previously published studies on workplace ETS exposure and CHD. Their argument that unreliable exposure assessment has obscured any workplace ETS/CHD risk is speculative and unconvincing. The shared diets and lifestyles of spouses has probably produced the weak association between spousal smoking and CHD reported in some spousal exposure studies.

Spouse related confounding factors are not introduced when workplace ETS exposure is used to define exposure (LeVois and Layard, 1994).

Response:

Since the publications by Steenland et al., and Glantz and Parmley, meta-analyses by He et al. (1999) and Wells (1998) have reported an association between workplace ETS exposure and increased risk of CHD. This association was statistically significant in Wells' analysis whether he looked at only what he considered the best studies (OR 1.50, 95% CI 1.12; 2.01), or all relevant studies including Steenland's ACS-II study (OR 1.18, 95% CI 1.04; 1.34). These analyses support a causal association between ETS exposure at work and CHD. However, the more significant consideration is total exposure to ETS combined from workplace, home and other sources. Studies that examine CHD risk in relation to measured cotinine levels better address this issue. A recent prospective study by Whincup et al. (2004) found increasing risks of CHD over 20 years of follow-up associated with increasing levels of serum cotinine: HRR 1.45(95% CI 1.01; 2.08) for 0.8-1.4 ng/ml; 1.49 (95%CI 1.03; 2.14) for 1.5-2.7 ng/ml; 1.57 (95% CI 1.08; 2.28) for 2.8-14.0 ng/ml.

Comment 78:

The current Draft Report directs similar criticisms at the study by Enstrom and Kabat (2003), a study that is based upon the California portion of the CPS-I study. Speculation about the possible bias due to background exposure and the use of vitamin pills is unconvincing. As pointed out by Dr. George Davy Smith in his BMJ editorial about the Enstrom and Kabat study (see quotes at the beginning of the lung cancer section of these comments) there are many valid reasons to suspect that the CPS-I subjects comprise a less biased sample than the CPS-II study subjects. In any event, the methods used in the CPS-II study are not very different, and introduce similar opportunities for misclassification of exposure. Enstrom and Kabat acknowledge that some spousal smoking exposure misclassification based upon the study intake questionnaire is likely. They collected additional follow-up lifestyle and exposure data, and employ a series of analyses to address this issue. Again, CPS-II also can not account for changes in smoking habits of the spouse.

Response:

In addition to concerns about background ETS exposures (see responses above), there are other concerns about the data and analysis presented by Enstrom and Kabat. For example, as pointed out by Thun (2003), the analysis appears to compare nonsmoking women married to smokers

with women exposed to ETS from other sources. In the 26 years of follow-up after 1972, no updated information was collected on the smoking status of the spouse. As a result many women were classified as exposed to ETS even though their spouse may have died, divorced or quit smoking. The resulting misclassification could substantially bias the results.

In Tables 2 and 3 of their paper, Enstrom and Kabat show a trend of increasing spousal smoking among individuals in the never-smoking groups with greater than 12 years of education. However, higher levels of education are generally associated with lower smoking rates (CDC, 2002) and lower exposure to ETS (Stamatakis et al., 2002). That the reverse was observed by Enstrom and Kabat calls these data or their analysis into question and suggests that a fair number of smokers may have been included in the never-smoking group. Such inclusion would obscure any association of ETS exposure and disease.

In Table 3 it is also apparent that the mean age of never-smoking women at enrollment decreased with increasing spousal smoking (53.7 yr at 1-19 cig/day; 49.8 yr at >40 cig/day). In addition, during the study period, mortality from CHD fell by about 5% every four years (NCHS, 2002). As a result, being younger, the women with higher spousal exposure benefited more from the overall decrease in CHD mortality compared with the older controls. Controlling for age alone would not be expected to adequately control for this interaction between age and time period of observation, again obscuring any ETS effects.

Comment 79:

The methods used in this study are reported by Enstrom and Kabat in detail, and are not accurately described in the Draft Report. For every study discussed in the Draft Report, not just the Enstrom and Kabat study, the Draft Report should include the author's own abstract prior to discussing the study (as was done by the U.S. EPA in their 1992 ETS report). In addition, key sections of the study methods and results should be presented as described by the authors. In the case of the study by Enstrom and Kabat this is especially important, as the Draft Report ignores important elements of the study methods and analysis that mitigate many of the criticisms. The principle investigators describe these features of their study:

> "The independent variable used for analysis was exposure to environmental tobacco smoke based on smoking status of the spouse in 1959, 1965, and 1972. Never smokers married to current or former smokers were compared with never smokers married to never smokers. The 1959 never smokers were defined as those who had never smoked any form of tobacco as of 1959. The 1965 never smokers were defined as 1959 never

> smokers who did not smoke cigarettes as of 1965. The 1972 never smokers were defined as 1959 never smokers who did not smoke cigarettes as of 1965 and 1972. The 1959/1999 never smokers were defined as 1959 never smokers who had never smoked cigarettes as of 1999. Never smokers married to a current smoker were subdivided into categories according to the smoking status of their spouse: 1-9, 10-19, 20, 21-39, =" src="/math/ge.gif" border=040 cigarettes consumed per day for men and women, with the addition of pipe or cigar usage for women. Former smokers were considered as an additional category. "

Response:

OEHHA, in both this and the previous review, provides a descriptive paraphrase of studies of interest rather than quoting authors' abstracts and methods verbatim. The reader with specific interests in a study's methodology will likely want to consult the original text.

Comment 80:

The Draft Report misrepresents these methods, claiming that misclassification is likely to be greater in this study than in other cohort studies of spousal smoking. In particular, the draft states that a 7% sample of the original 9,619 nonsmokers is too small, and ads little assurance about the validity of the exposure measure. Just the opposite is the case. This follow-up provides more assurance about the validity of the exposure measure than is provided in most spousal smoking cohort studies. It is an important validity check that has not been accurately described. The description provided by Enstrom and Kabat should be included:

> "The personal and lifestyle characteristics and follow up status for 1959 never smokers were relatively independent of their spouse's smoking status (tables 2 and 3). Also, the baseline characteristics of the 1999 respondents in 1959 were similar to those for all participants in 1959, except for a younger age at enrolment. Although heavily censored by age, the 1999 respondents seemed reasonably representative of survivors. Race, education, exercise, height, weight, and fruit intake had also remained largely unchanged among the 1999 respondents since 1959. The proportion of participants who had withdrawn as of 1972, were lost as of 1999, or had an unknown cause of death was not related to the smoking status of spouses. However, widowhood (widowed as of 1999) increased substantially with the level of smoking in the spouse."
>
> "The smoking status of spouses as of 1959 was related to three self reported measures of exposure to environmental tobacco smoke as of 1999 (table 4). Particularly for women, there was a clear relation between smoking status of spouses as of 1959 and self reported measures in 1999 of having lived with a smoker, having lived with a smoking spouse, and a positive answer to the question "In your work or daily life, are (were) you regularly exposed to cigarette smoke from others" Also, the percentage of participants currently married as of 1999 declined substantially with the smoking status of the spouse, owing to increased widowhood. Smoking history of the spouse as assessed in 1999 was strongly

related to exposure to environmental tobacco smoke as of 1999 for both men and women (table 5)."

Enstrom and Kabat anticipate criticisms that have been repeated in the Draft Report, and they address these criticisms in their paper. Their greater understanding of the CPS-I data and underlying issues is ignored. Again, in order to present an accurate description of the study the authors own words should be included in the discussion of their study.

Strengths of study

"CPS I has several important strengths: long established value as a prospective epidemiological study, large size, extensive baseline data on smoking and potential confounders, extensive follow up data, and excellent long term follow up. None of the other cohort studies on environmental tobacco smoke has more strengths, and none has presented as many detailed results. Considering these strengths as a whole, the CPS I cohort is one of the most valuable samples for studying the relation between environmental tobacco smoke and mortality."

"Concern has been expressed that smoking status of the spouse as of 1959 does not accurately reflect total exposure to environmental tobacco smoke because there was so much exposure to non-residential environmental tobacco smoke at that time.[6] The 1999 questionnaire showed that the smoking status of spouses was directly related to a history of total exposure to environmental tobacco smoke. It also showed that the extent of misclassification of exposure was not sufficient to obscure a true association between environmental tobacco smoke and coronary heart disease among women (see tables 4 and 5)."

"Our methodology and results are fully described because of concern that the earlier analysis of coronary heart disease in CPS I [10] was flawed by author bias owing to funding by the tobacco industry.[4] Our results for coronary heart disease and lung cancer are consistent with those of most of the other individual studies on environmental tobacco smoke,[4–8] including the results for coronary heart disease and lung cancer in the full CPS I.[10 16] Moreover, when our results are included in a meta-analysis of all results for coronary heart disease, the summary relative risks for current and ever exposure to environmental tobacco smoke are reduced to about 1.05, indicating a weak relation."

"Widowhood was strongly correlated with smoking status of spouses, owing to the reduced survival of smokers. Since widowers have higher death rates than married people,[22 23] controlling for widowhood would be expected to reduce the relative risks in this and other studies of smoking in spouses. The precise effect of widowhood due to smoking in spouses still needs to be determined, but it may partially explain the positive relative risks found in other cohorts."

Response:

Aside from the editorial decision generally not to include text verbatim from the cited papers, OEHHA has reservations about the authors' data interpretation. The tables to which the

commentator refers are somewhat confusing making it difficult to verify the authors' assertions. Under the heading of "regular exposure to cigarette smoke from others in work or daily life", the numbers presumably refer to exposures that exclude the spouse, but this is not explicitly stated. Also it is not clear whether the category of "lived with smoking spouse" is separate from or a subset of "lived with smoker". These distinctions have bearing on the association of ETS exposure and spousal smoking status. The data in the tables could be interpreted to indicate that there were significant non-spousal exposures to ETS, in which case the use of spousal smoking status as the only measure of exposure would lead to substantial misclassification. Also, the authors have not made a convincing case that background ETS exposure was not a problem.

Comment 81:

The weight of evidence of a causal connection between ETS exposure and heart disease has gotten increasingly weaker, not stronger. Epidemiological studies that undermine the conclusion that there is a relationship are systematically criticized and ignored in the Draft Report in order to draw conclusions that are not supported by the consideration of all data. Laboratory studies are presented as if they merit equal consideration with the epidemiological studies, and are interpreted as if they describe a convincing mechanism for producing the unlikely 30% risk increase favored by the Draft Report. Those data are presently impossible to interpret. The exposure conditions are not realistic, the specificity of the endpoints is not known, and it is not known if the physical and chemical endpoints actually cause heart disease under realistic exposure conditions.

Response:

OEHHA disagrees that the weight of evidence for a causal association between ETS exposure and heart disease has gotten weaker. Newer studies, both epidemiological and laboratory, continue to provide evidence for this association. For example, a recent population-based prospective study by Whincup et al. (2004) found significant associations between cotinine levels and CHD risk with significant dose-response trends even after adjustment for other cardiovascular risk factors. The prospective nature of this study and its use of cotinine levels as a measure of ETS exposure address many of the concerns relating to bias and misclassification, and strengthens the evidence for a causal association. As described in our response to a comment above, a recent laboratory study by Wong et al. (2004) exposed fibroblasts to media containing whole sidestream smoke or whole mainstream smoke. The exposure to sidestream smoke was at nicotine concentrations (~2 µg/ml) adjusted to reflect typical tissue nicotine levels

in nonsmokers following exposure to ETS in a smoky room. In cells exposed to media with sidestream smoke, the endoplasmic reticulum, Golgi apparatus, and distribution of the chemokine cIL-8 were markedly more affected than in control cells and in those exposed to mainstream smoke. This study documents a differential response of cells to sidestream versus mainstream smoke. The presentation of both study types here and in the main document is not meant to reflect the relative importance of the kinds of studies but rather that both lines of investigation contribute to the body of evidence linking ETS exposure and CHD. While it is true that the results of some studies may be difficult to interpret at this time, that is often an indication of the incompleteness of our understanding of the biological interactions, not that the interactions do not exist.

Comment 81:

CONCLUSIONS

In each section of the Draft Report addressed in these comments there is a consistent effort to emphasize data that support the conclusions of the report, and criticize and ignore data that undermine those conclusions. As a result, in each section I have tried to note misrepresentations of the data and correct the record by discussing the null studies and data that are passed over in the report. As suggested above, a far better format would be to include much more detail about each study in the words of the authors before embarking on subjective evaluations and conclusions about strengths and weaknesses. Most readers will not have read the underlying papers. They need full disclosure about the studies, their methods and results, not just thumbnail sketches that are too easy to reshape to conform to the "weight of evidence".

Criteria used by the U.S. EPA to evaluate the quality of human epidemiologic research data, as cited and discussed above, should be used in the Draft Report instead of the vague and subjective criteria that the draft claims to have used. Each study that is described and evaluated in the Draft Report should be judged by these criteria. Tables should also be created that summarize the strengths and weaknesses of each study with respect to these uniform criteria.

The magnitude of concern about underlying problems of bias and confounding in epidemiological studies should be inversely proportional to the weakness of the association. By that standard, we need a quantum level of improvement in study methods and design to resolve questions about the weak spousal smoking associations. None of the studies discussed in the Draft Report provide such an improvement, although the large IARC lung cancer study comes close. Weak associations can only be studied using large samples and valid and accurate methods that address all of the important issues of bias and confounding. Conducting and/or pooling the results of an ever-increasing number of small studies that all use the same basic flawed design, and that can not adequately address possible bias and confounding, will never resolve the issue.

Response:

OEHHA stands by the conclusions in the draft report that there is a causal association between ETS exposure and heart disease. As noted earlier in our responses to these comments and others, there are a number of studies demonstrating statistically significant associations, particularly where exposure ascertainment was relatively better. Furthermore, a number of laboratory studies provide data supporting biological plausibility.

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