State of California
AIR RESOURCES BOARD

APPENDIX III

PROPOSED IDENTIFICATION OF ENVIRONMENTAL TOBACCO SMOKE AS A TOXIC AIR CONTAMINANT

PART C – PUBLIC COMMENTS AND ARB/OEHHA STAFF RESPONSES

As Approved by the Scientific Review Panel
On June 24, 2005

The SRP approved Part C is a supporting technical document which is incorporated by reference in the Initial Statement of Reasons (Staff Report)

State of California

Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant

Part C: Public Comments and ARB/OEHHA Staff Responses

As Approved
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on June 24, 2005

California Environmental Protection Agency
Air Resources Board
Office of Environmental Health Hazard Assessment

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Note:
The content of this comment is accurately characterized by OEHHA, but unfortunately the original comment is unavailable.

I.

Air Resources Board Staff Responses to Comments on the Draft ETS Report Part A

SUMMARY AND RESPONSES TO COMMENTS SUBMITTED ON THE ENVIRONMENTAL TOBACCO SMOKE DRAFT REPORT

Part A (Exposure Assessment)

Comments and the Air Resources Board's (ARB) staff responses on exposure assessment (Part A) of the "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant Draft Report, December 2003."

Coalition from the Natural Resources Defense Council, Breast Cancer Fund, San Francisco Bay Area Physicians for Social Responsibility, Los Angeles Physicians for Social Responsibility, March 29, 2004
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William V. Corr, National Center for Tobacco-Free Kids, March 29, 2004
Susan Rappaport and Paul Knepprath, American Lung Association, March 29, 2004
Robert T. Croyle, Ph.D., Director, Division of Cancer Control and Population Sciences, National Cancer Institute – March 29, 2004

1. Comment: In general, we support the conclusions of the draft report and ARB's action to identify ETS as a TAC.

Response: We appreciate your comment.

James Repace, March 5, 2004

1. Comment: As you know, there have been few measurements of ETS in outdoor microenvironments, and to the best of my knowledge, there are no data on outdoor carcinogen levels of ETS. I have collected indoor/outdoor particulate PAH data while on a cruise ship in the Caribbean. A preliminary report on this data is available.

Response: We agree. There are few studies done on the carcinogenic components of ETS in the outdoor air. We will incorporate the results of your study as soon as it is a published peer reviewed document.

R.J. Reynolds Tobacco Company, March 25, 2004

1. Comment: The current California Environmental Protection Agency 2003 Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant," does not support designation of environmental tobacco smoke (ETS) as a toxic air contaminant (TAC) in California. Specifically, Sections 39650-39674 of the California Health and Safety Code set forth several requirements that the Agency must meet before designating a substance as a TAC. For example, Section 39660 initially requires Cal/EPA generally to assess the exposure and health effects data for the substance and to specifically determine whether current California ETS exposures are responsible for adverse health effects, then to provide an estimate of the exposure level that may cause or contribute to adverse health effects in California.

Response: California Health and Safety Code Section 39660(a) states specifically that "Upon the request of the state board, the office, in consultation with and with the participation of the state board, shall evaluate the health effects of and prepare recommendations regarding substances, other than pesticides in their pesticidal use, which may be or are emitted into the ambient air of California and that may be determined to be toxic air contaminants." (underline is added for emphasis). A toxic air contaminant is defined in the Health and Safety Code, Section 39655 as "an air pollutant which may cause or contribute to an increase in mortality or in serious illness, or which may pose a present or potential hazard to human health." We believe there is sufficient evidence presented in the draft report (Parts A and B) to show that ETS is emitted into the ambient air in California and that there are various adverse health impacts associated with exposures to ETS.

Furthermore, Health and Safety Code section 39660(c) states that the evaluation shall also contain "an estimate of the levels of exposure that may cause or contribute (underline is added for emphasis) to adverse health effects in California." In Part A, Chapter V, a scenario approach was used to estimate possible ranges of public exposure to ETS. While we recognize that some of the public's exposure is very low, other people's exposures are higher as they go near the smoking public. Health and Safety Code section 39660.5 requires that ARB assess exposures in indoor environments as well as in ambient air.

Brian McGinn, Lorillard Tobacco Company, March 25, 2004

1. Comment: Personal monitoring studies provide the most reliable basis for measuring ETS exposure.

Response: As you are aware, fixed ambient monitoring is the basis of most outdoor air quality measurements. We believe our exposure assessment is representative of personal outdoor exposure for two reasons: 1) our ETS measurements were collected in the breathing zone on the edges of outdoor smoking areas where non-smokers also could have been exposed to ETS, and 2) our multiple exposure scenarios included periods of the day away from ETS exposure, as would be the case with personal exposure monitoring.

2. Comment: The ARB draft report largely ignores the findings of an Oak Ridge study of personal monitoring of ETS in 16 U.S. cities.

Response: The 16-city study (Jenkins *et al.,* 1996) was referenced in the biomarker section of Chapter V of the report, but not in our section on page V-6 about other air monitoring for ETS. Staff will add a reference to this study in the monitoring section on page V-6.

3. Comment: The field and trip spikes were prepared at only one level per study location (ranged from 10 to 400 micrograms of nicotine) and these levels were considerably higher than actual field samples, making these spikes inappropriate for evaluating the accuracy of measured air concentrations.

Response: The method detection limit for nicotine was based on lab spikes of 0.1 microgram of nicotine. Most field samples contained concentrations of nicotine above the method detection limit. The field and trip spikes were prepared at a higher concentration to ensure that there was no breakthrough in the sampling tubes. While it would have been interesting to have prepared field and trip spikes at more than one level (with one level closer to anticipated field concentrations), the monitoring budget was too limited. We do not believe that the lack of these data limit the use of the measured air concentrations.

4. Comment: Only a few, unrepresentative outdoor locations were used for monitoring, sites that appear to have been selected arbitrarily or to represent maximum potential exposures.

Response: Sites were selected to represent a variety of outdoor exposures near ETS. The results of the monitoring indicate a range in outdoor concentrations of ETS.

5. Comment: Monitoring was conducted only in, or immediately downwind and adjacent to, designated smoking areas, which can be readily avoided by non-smokers and, thus, are not representative of typical ETS exposures in the ambient air.

Response: While it is true that monitoring was conducted adjacent to designated smoking areas, we do not agree that non-smokers could always avoid these exposures. Following is a summary of the exposures at the locations

where monitoring was conducted: 1) At the airport smoking area where monitoring was conducted, the only exit from the baggage claim area passed through the outdoor smoking area. Arriving passengers were witnessed standing near the smoking area while they waited to be picked up. 2) At the community college where monitoring was conducted, smoking was allowed at an eating area outside of the cafeteria. If a student or faculty member chose to eat outdoors, they could be exposed to ETS. 3) At the two office buildings where monitoring was conducted, smoking was allowed outdoors. Upon entering or leaving the building, sitting outside for a break or lunch, or using an ATM machine, there was potential for exposure to ETS. 4) At the amusement park smoking area where monitoring was conducted, the designated area was centrally located near main walkways. Some parents brought their children into the smoking area, as witnessed by our monitoring staff.

6. Comment: The ARB study was an area monitoring study that did not measure exposure duration or the level of exposure to particular individuals. Personal monitoring data is preferred over area sampling.

Response: The purpose of the monitoring study was only to gather ambient data. The study was not an individual exposure assessment. See response to comment #5 above.

7. Comment: The ARB study used nicotine as the marker for ETS exposure. There are shortcomings with the use of nicotine as an ETS marker. The dilution of ETS emitted in outdoor air, combined with possible absorption to outdoor surfaces in proximity of smokers, renders risk estimation of outdoor exposures based upon nicotine problematic. The report mischaracterized a paper by LaKind *et al*. regarding 3-EP as a marker and should rephrase this section.

Response: The ARB monitoring used nicotine as a marker for ETS because, based on information we reviewed, we believed there would be less adsorption to outdoor surfaces than indoor environments, where adsorption has been documented as a problem with using nicotine as a marker. We agree that dilution of ETS emitted in outdoor air, especially on windy days as were experienced at three of the monitored locations, may have resulted in lower ETS concentrations than would have been measured with less dilution. However, these measurements were representative of realistic exposure. Nicotine was also chosen as a marker because of its relative ease with regard to sampling and analysis. We did not intend to mischaracterize the LaKind *et al*. paper's discussion of the value of 3-EP as a marker for nicotine. We will delete the sentence in question that inaccurately refers to 3-EP on page V-6 of the report.

8. Comment: The ARB air monitoring study has not been published in a peer-reviewed scientific journal.

Response: The ARB has not typically published results of an air monitoring study for a candidate TAC, prior to identification of the candidate as a TAC. Peer review of the report, which includes the details of the air monitoring study, is provided by the Scientific Review Panel on Toxic Air Contaminants. In addition, comments are received from other agencies and the public. Many of the individuals that submitted comments are experts in their respective fields (e.g., exposure assessment).

9. Comment: Under the Tanner Act, passed in 1983, the ARB has authority to identify and adopt control measures for "toxic air contaminants." The ARB is limited to regulate based on ambient or outdoor air and has no authority to regulate indoor air or to rely upon indoor air exposure levels as a basis for regulation of outdoor air.

Response: California's air toxics law, Assembly Bill 1807 (sponsored by Tanner) established ARB's authority to identify and control toxic air contaminants in California. The law requires the ARB to first establish if a substance is toxic and to what extent. This step is called the risk assessment or identification phase of the process. In this process, the ARB is required to evaluate the exposures in indoor environments as well as in ambient air conditions (Health and Safey Code section 39660.5). Once a substance is determined to be a toxic air contaminant by the ARB, it enters into the next step of the program. This step is called the risk management or control phase of the process. In this phase, the ARB is required to evaluate the possibilities of reducing exposures to TACs in consideration of costs and risk as well as a number of other factors (Health and Safety Code sections 39665 and 39666).

The evaluation of ETS as a TAC falls under the first step, risk assessment. This rulemaking effort is a proposal to identify ETS as a TAC in California. Therefore, no control measures are being proposed as part of the risk assessment process at this time to reduce public exposure to ETS.

See response to comment #1 by R.J. Reynolds Tobacco Company, which is incorporated by reference here, for a discussion of authority to identify substances as TACs.

10. Comment: The draft exposure assessment does not demonstrate a meaningful level of outdoor ETS exposure. In view of the limited data on outdoor ETS exposures and the localized nature of such exposures, the ARB lacks a reliable scientific basis to conclude that ETS exposures in the outdoor environment in California are of sufficient intensity, duration or scope to justify listing ETS as a TAC.

Response: Under State law, the ARB is to identify a substance as a toxic air contaminant if it determines the substance is "an air pollutant which may cause or contribute to an increase in mortality or increase in serious illness, or which

may pose a present or potential hazard to human health." Under this same law, an air pollutant may include groups of substances such as soot, gases, particulate matter, smoke, or any combination (Health and Safety Code section 39013).

Under State law, the ARB must show that Californians are exposed to ETS and that exposures to ETS may cause or contribute to adverse health effects (Health and Safety Code section 39657, 39660 et seq.). The Part A (exposure assessment) document shows that the public is exposed to ETS in California outdoors and the OEHHA's Part B (health assessment) document shows that exposures to ETS at different levels results in several different adverse health effects. See responses to comments #1 by R.J. Reynolds and comment #9, which are incorporated by refernce here.

11. Comment: The ARB's ETS exposure assessment is inconsistent with the U.S. EPA's Final Guidelines for Exposure Assessment (U.S. EPA, 1992)

Response: The ARB is required by law to evaluate exposures to and emissions of potential toxic air contaminants. The State is not required to follow U.S. EPA's Guidelines for Exposure Assessment (see Health and Safety Code Section 39656). The two programs are separate and are different both in scope and purpose.

12. Comment: The Rogge *et. al*., (1994) study referred to in Chapter V of the exposure assessment is outdated and fundamentally flawed. Smoking rates have declined and smoking patterns have changed since the original study in 1982.

Response: We agree that the information presented in the Rogge study is outdated. Smoking rates have declined since the date of the Rogge *et al*., 1994 study. We state this clearly in Chapter II (pages II-2), Chapter IV (pages IV-4 and IV-5, IV-9 and IV-10) and Chapter V (pages V-4, V-11, and V-31 and V-32). This study, along with others, was used for comparison purposes only and presented a source apportionment approach of estimating outdoor concentrations of ETS. In addition, the Rogge study was included to address our requirement to consider all available data when identifying a substance as a TAC.

13. Comment: The outdoor exposure levels calculated in the Exposure Chapter are based exclusively on a 2003 ARB air monitoring study.

Response: Chapter V of the Part A report, includes studies by Rogge *et al.,* 1994, Eisner *et al.,* 2001 and Schauer *et al.,* 1996 (see Chapter V, pages V-6 through V-13). Since there are relatively few data on outdoor ambient concentrations, the ARB ambient monitoring results from its ETS study were used, in part, as the outdoor ambient concentration input to the exposure

scenarios (see Chapter V pages V-34 through V-47). The scenario-based approach to estimate a person's daily exposure to ETS uses several estimates of exposure from different microenvironments. One of these includes an estimate of outdoor levels of ETS.

14. Comment: In almost all previous TAC exposure assessments, the ARB relied upon California population-weighted exposures to outdoor average ambient concentrations of the candidate substances. By contrast, the ARB has relied exclusively upon localized short-term exposures, in or immediately downwind and adjacent to, designated smoking areas, data that have no relevance to general long-term ETS exposure in the ambient air in California.

Response: As stated in Chapter V, page V-1, A scenario-based approach was used to characterize the range of the public's exposure to ETS in this report. This approach differs from previous TAC exposure assessments, which were based on California population-weighted exposures to outdoor average ambient concentrations. That approach was appropriate for TACs emitted from area-wide or region-wide sources such as motor vehicles and industrial plants. However, cigarettes and cigars, the primary sources of ETS, are smaller sources that emit pollutants near people, and ETS is not monitored at ambient monitoring stations like most other previously identified TACs (See Chapter V-5 for reasons why ETS as a whole cannot be measured). Staff did include an estimate of an urban background level to Chapter V of the draft report for illustration purposes. The text was included in subchapter C, section 5. A more detailed discussion was newly included to the draft report as appendix D.

This is not the first time the ARB has taken this approach. For example, there is no population weighted exposure assessment for vinyl chloride. Exposures, in this case, occur near localized specific sources and such "hot spots" data was used in the TAC exposure assessment. Also, there is interest in short-term exposures to ETS as well as long-term exposures. There are adverse health effects associated with both durations of exposures.

15. Comment: The ARB's scenario-based approach is an inadequate basis to demonstrate outdoor exposure to ETS.

Response: As stated in Chapter V of the report, the scenario-based exposure method uses the results from ARB's ETS air monitoring study, available indoor ETS concentration data, and scenario-based activity patterns to estimate exposures under different conditions. ARB's scenario-based approach is intended to provide a "snapshot" of what some subpopulations ETS exposure might be. We believe this approach provides the best estimated range of exposures a person, adult or child, may experience each day. See also response to comment #13. In addition, staff estimated a statewide outdoor urban background level of ETS as mentioned in response to previous comment #14.

See response to comment #1 by R.J. Reynolds Tobacco Company for a discussion on Health and Safety Code requirements for evaluating exposures to potential TACs.

16. Comment: All prior TAC listings have been based on more extensive and reliable exposure data than that available for ETS. The draft report does not identify the number of people exposed to ETS in the ambient air in California, or the duration or level of such exposure.

Response: We dissagree that all prior listings have been based on more extensive and reliable exposure data. In this report, we present several measurements of ETS concentration data as well as smoking prevalence data (see Chapter V). In the scenarios, we provide estimates of duration and level of exposure (Chapter V-34 through V-48). Refer to response to comment #14 with regard to why we did not feel a population-weighted exposure assessment was appropriate for ETS.

17. Comment: ARB has failed to characterize the intensity, duration or frequency of ETS exposure in outdoor air, and failed properly to characterize the exposed population.

Response: See response to comments #14, #15 and #16 above.

Roger A. Jenkins, March 16, 2004

1. Comment: The report ignores key available data that is California-specific. The report relies on modeling studies of exposure rather than relying on direct measurement of exposure.

Response: We have included California-specific data in Chapter V of the Part A report. In addition, our scenario-based exposure approach uses measured concentration results from several studies, including California-specific studies, along with California-specific activity patterns to estimate a range of possible daily public exposures to ETS. The purpose of our personal exposure estimate was to provide a more realistic estimate of public exposure under various scenarios.

Data from direct measurements of exposure are found in Chapter V, page V-48, Biological Markers of Exposure to ETS. Likewise, California-specific data was included in this section. The commenter did not submit key data on either ETS exposure modeling or measurement studies for our consideration.

2. Comment: Criticism, either direct or thinly veiled, is leveled at some but not all of the studies. This provides an unnecessarily advocative tone to the Report, which seriously diminishes its credibility. If the authors believe that an analysis of

the strengths and limitations of studies are useful to the discussion, then such an analysis must be performed on all of the studies considered for discussion.

Response: We believe we have presented a balanced assessment of the studies used in our report.

3. Comment: No analysis was performed on the only California-specific data set available for personal exposure to nicotine and salivary cotinine levels, despite the fact that such data has been publicly available for years.

Response: The commenter is not specific as to what data set was referenced in the peer-reviewed literature. To the extent that they are based on the design used for the rest of the 16 Cities Study, we have the same concerns about the data and potential bias mentioned in the response to comment #5 below.

4. Comment: There is discussion of biomarker levels in smoking mothers, but no effort is made to rationalize its connection with the topic of section: biomarkers and ETS exposure.

Response: See responses to comment #14 below.

5. Comment: There are no substantive conclusions for this section with regard to the stated objective (page V-50) to examine "the utility of biomarkers to assess the extent of exposure to ETS." The "conclusion," that cotinine in body fluids can be used to distinguish smokers from ETS exposed individuals, is hardly a quantitative assessment, and ignores key scientific findings in the area. These are a) overall indicators of exposure (number of cigarettes observed to have been smoked near subjects, smoking/non-smoking home/workplace classification groupings, etc, show proportional increases in cotinine levels for increasing nicotine exposure when data from individuals is composited into larger groupings. (This may be due to dampening of individual differences in metabolism.); b) individual cotinine levels, while having statistically significant correlations with nicotine exposure, appear to have little *quantitative* predictive capability (in other words, one cannot use cotinine level to quantitatively predict an individual's exposure to within a factor of 2, or even 5); c) models based on metabolism of nicotine by smokers appear to be unable to quantitatively estimate the magnitude of inhaled dose of nicotine; and d) other biomarkers of tobacco specific constituents, such as tobacco specific nitrosamines, may ultimately be useful for qualitative or even semi-quantitative indicators of inhaled ETS dose. However, the analytical challenges of measuring extremely trace quantities of these markers in biological fluids are preclude their applicability to broad studies of ETS dose at this time.

Response: We agree that many of the biomarkers examined in this section are not particularly useful for measuring ETS exposure at this time for reasons given in the comment and in the text of the document. However, the commenter's

objections not withstanding, at this time nicotine and cotinine represent reasonable markers of tobacco smoke exposure. For this reason we have concentrated on measurements of nicotine and cotinine as the best currently available measures of ETS exposure.

6. Comment: On Page V-54. The 16 Cities Study was not performed by LaKind *et al.*. The 1999 manuscript is a further analysis of the data reported first (and conducted by) Jenkins *et al.*, 1996. If it is important to provide the reader with funding sponsorship or affiliation of authors, then full disclosure should be made for all authors cited: eg. Smith et al., 2005 well-recognized anti-smoking advocates, reported …… Frankly, if the data have been reported in the peer reviewed literature, sponsorship or the personal preferences of the authors should not be considered in the analysis. Period. Also, Dietrich Hoffmann's name is incorrectly spelled at the bottom of the page.

Response: The text has been re-worded to eliminate references to funding source. We have also corrected the spelling of Hoffmann and clarified LaKind's role regarding analysis of data from the 16 Cities Study.

7. Comment: On page V-55. The statement that the EPA had raised a multitude of concerns (unspecified) regarding the 16 Cities Study in some post hearing commentary in February of 1996, when the peer-reviewed manuscript was not even published until December 1996, suggests that the authors are bending over backward to appear as advocates, rather than dispassionate, unbiased assessors of the scientific data.

Response: Although not specified in the comment, the post-hearing commentary to which the commenter refers is probably Repace's invited analysis of comments to the OSHA docket regarding an indoor air rulemaking concerning ETS. This analysis raised questions regarding the credibility of the reported workplace nicotine levels presented as data collected in the 16 Cities Study. Specifically, it suggests that the reported values are far lower than would be expected for an office workplace, and are lower than would be predicted based on the study's associated salivary cotinine levels.

Our own examination of the published report also led to concerns about how representative the data are. For example, compared to the general population, the study population is disproportionately female (68% vs 53%), better educated (79% had at least some college education vs 47% in the general population), of higher socioeconomic status (70% had income = $30,000/year vs 50% in the general population), and biased towards professional employment (only 12% were in the categories of service, production and crafts, operators, laborers and fabricators, or other compared to 42% for the general population). These are all characteristics associated with that portion of the population that tends to have lower exposure to tobacco smoke. It appears that in the study group, only 13% had actual ETS exposure. These characteristics of the study group would tend

to bias the results towards no effect. Our concerns regarding the validity of the data, not an advocacy position, are the reasons we chose not to include the 16 Cities Study in this update.

8. Comment: Also, it should be noted that the 16 Cities Study reported personal exposures, and the work described in Hammond *et al*., 1999 are area concentrations of ETS nicotine. As such, the two data sets are not comparable.

Response: The text has been amended to show that Hammond's measurements are of area concentrations. However, as shown in Figures 2 and 3 of Jenkins and Counts (1999), there appears to be a reasonably linear relationship between area and personal monitoring for nicotine, at least among restaurant servers and bartenders. It is likely that a similar relationship exists for office measurements as well.

9. Comment: Finally, the statement is made that personal exposure nicotine concentrations reported by Phillips *et al*., 1998 in Prague are lower than in comparable studies. The reference to comparable studies is unclear. Do the author's mean compared to Phillips' other studies (most of which have, inexplicably, not been even cited by the report). Do the author's mean lower than the US 16 Cities Study? Whatever studies that are considered truly comparable to the Phillips work (large number of subjects, careful segregation of exposure types, breathing zone personal monitoring) need to be specifically cited here.

Response: The workplace nicotine data reported by Phillips *et al.,* 1998 for Prague are lower than those reported by Phillips and Bentley (2001) for Bremen (arithmetric mean 1.1 µg/m3 versus 1.9-2.4) using comparable techniques. They are also lower than the range of workplace measurements (2-8 µg/m3) reported in Table V-9 of the document that includes area measurements by Hammond (1999). Although personal breathing space and area monitoring are not strictly comparable, as mentioned in the response to comment #8, the two measures appear to be reasonably linearly correlated. The text has been modified to identify studies to which Phillips *et al*., 1998 is compared.

10. Comment: On page V-58. "The …. validity of workplace nicotine levels has been challenged…" Which workplace nicotine levels? Those reported by Phillips for Prague? If the authors want to critique individual studies, then the criticism needs to be spelled out and it needs to be done for all studies that are included in the data analysis. My suspicion is that the authors are referring to a criticism of the 16 Cities Study (Jenkins *et al.,* 1996) published many months prior to the publication of the peer-reviewed manuscript. To include such comments without specifying the criticism gives a tone of apparent bias to the entire Report. Also, despite the fact that the data from the 16 Cities Study for Fresno (nicotine exposure and salivary cotinine levels that could have been analyzed) has been available for years (see the last page of Graves *et al.,* 2000,

or http://www.ornl.gov/sci/csd/Research_areas/ecms_rd_etsce_16cities.html), the authors of the Report did not analyze that data.

Response: As the commentor suspects, the workplace nicotine levels to which the sentence refers are those in the 16 Cities Study presented on the OSHA docket regarding an indoor air rulemaking in 1996. These are described in the responses to comment #7 above.

11. Comment: Finally, the analysis by LaKind *et al*., 1999 of salivary cotinine levels from the 16 Cities Study shows median salivary cotinine levels for subjects only exposed in the workplace (Cell 3, Table V-15) of 0.347 ng/mL. When corrected for typical differences between saliva and serum cotinine levels, the levels reported by Pirkle *et al.,* 1996 for subjects exposed only in the workplace would be 0.40 ng/mL. To report a criticism of the 16 Cities Study by EPA regarding workplace nicotine levels, and then have the actual cotinine values reported by two independent groups be nearly indistinguishable makes no sense. This sort of biased data presentation jeopardizes the credibility of the Report, and calls other conclusions by the authors of the Report into question.

Response: The cotinine levels presented in LaKind *et al.*, 1999 reportedly represent the average of two measurements, one taken the evening before a 24-hour workplace measurement period (approximately one-half day), and the second, 24 hours after the workplace measurement period. As the authors recognize, a substantial fraction of the cotinine derived from workplace ETS exposure may have been excreted prior to the second measurement. The implication is that the actual workplace nicotine exposures may have been larger than suggested by the cotinine measurements. For individuals with ETS exposure in the workplace but not at home, whether or not the first cotinine sample was taken after a workday or after a weekend day could substantially alter the measured cotinine levels. It is thus unclear how well the median value of 0.347 ng/ml reported by LaKind reflects work exposure, and how this compares with Pirkle's geometric mean value of 0.318 ng/ml. Our concerns regarding the nicotine measurements remain.

12. Comment: On page V-59. The original data analysis of salivary cotinine and nicotine exposure from the US 16 Cities Study (Jenkins and Counts, 1999b) is not even cited in the references for the chapter. Also, the presentation of the cotinine data from NHANES III, reported in Pirkle, (1996), even though it is segregated such that it would be directly comparable to that reported by LaKind *et al.*, 1999 is missing from this analysis.

Response: The reasons for not including the 16 Cities study are addressed above in responses to comments #7 and #11.

13. Comment: In addition, the whole body of Phillips' work (eg, Phillips *et al.*, 1998, etc) is not referenced or discussed in the Report. This one page affords

several examples of inadequate literature review, reporting and analysis of the applicable scientific literature for this Report. It would be easy for the reader to draw the conclusion that if *these* key studies are not considered, *other* key investigations in other parts of the report have been ignored.

Response: Contrary to this commenters assertion, Phillips' work is cited or referred to several times, on pages V-55 thru V-58.

14. Comment: On page V-65. The authors need to clarify the relevance of maternal smoking biomarkers to the topic being discussed in the Report. Such is not evident on this page.

Response: Prior to the section in question, the report discusses various compounds, their utility as biomarkers of exposure, and their relative levels in adults. Arguably the discussion of maternal exposure to smoking could have followed at the end of section 3: Analytical methods for nicotine/cotinine. However, inasmuch as the exposure to smoke components in utero represent a more complex exposure scenario compared to that of an adult, it was decided that a separate section following the discussion of biomarkers in adults was appropriate.

15. Comment: In Chapter V of the report, there is a discussion as to **"**exposure to smokers" by considering the time spent around smokers. However, no data is presented to support the contention that time spent around smokers, or the detection by the human that they have been exposed to ETS, results in exposures that are relevant from a clinical or health standpoint. To mention exposure without detailing the effects of such exposure is irrelevant. To simply say that a person is exposed provides no useful information, because no perspective on the degree of exposure is provided.

Response: The ARB and OEHHA are required by Health and Safety Code Sections 39660 *et seq*. to evaluate the health effects of and prepare recommendations regarding substances which may be emitted into the ambient air in California. The draft report as a whole (Parts A and B) clearly shows that there are exposures to ETS in California and that there are adverse health effects associated with ETS exposures.

16. Comment: The comment is made that solanesol can not be a good marker for ETS outdoors because it degrades in sunlight is misleading since many other ETS constituents do as well. Based on National Academy of Sciences criteria for good markers, it would sound like solonesol would do a good job tracking those constituents that degrade in sunlight. The report should also consider that under standard protocols for analysis of nicotine and 3-EP, 4-EP eludes at essentially the same time and has been used by several laboratories for a standard.

Response: Our purpose was to show what markers have been used and what researchers have said about those markers. We did not use these markers in our analysis of exposure.

17. Comment: In a study by Djordjevic *et al.*, 2000 it is unclear how a discussion of carbon monoxide (CO) in mainstream cigarette smoke relates to ETS emissions.

Response: The Djordjevic study compared mainstream smoke from a Federal Trade Commission (FTC) machine-smoking test method to mainstream smoke generated by an actual smoker. Although ETS consists of thousands of compounds, the Djordjevic study focused on the mainstream smoke content of CO, nicotine, and tar from the FTC machine-smoking test method and actual smokers. The results presented in our report indicate that the results from both the machine-tested mainstream smoke (nicotine, tar, and CO) and the actual smoker are similar, although slightly lower for the FTC machine-smoking test method. We believe that these three compounds are a good comparison to what might be seen overall in ETS emissions.

18. Comment: There is a lack of data comparing ETS emissions with other sources regarding CO, nicotine, and RSP.

Response: The report has been revised to provide perspective on the contribution to ETS emissions on the statewide emission inventories.

19. Comment: It is unclear how ambient ETS emissions were calculated since all cigarettes are assumed to be smoked outside.

Response: Ambient ETS emissions are primarily based on California's cigarette distribution and emission factors (see Appendix B, Part A). Because no studies exist to quantify ETS emissions, ARB staff opted to estimate an indoor and outdoor upper limit. However, the report has been revised to further clarify the relative difference between indoor and outdoor ETS emissions.

20. Comment: Evidence is provided in the report to indicate that the constituents of ETS begin to react and decompose within short periods of time following their emission into the ambient environment. Clearly, ETS in ambient air in sunlight for any important length of time is no longer ETS. And yet the report, provides no justification or rationale as to why the use of existing regulations that establish safe concentrations of many of the compounds of interest in ETS is not an appropriate approach.

Response: In the report, we characterize ETS as a mixture of several thousands of compounds and recognize that complex chemical reactions take place immediately upon formation of ETS. However, it is the exposure to the entire mix that has been related to adverse health outcomes in many

epidemiological studies. From an exposure perspective, it seems clear that the public is exposed to the "mixture" of ETS. So, it is reasonable to consider ETS as a whole and not on the basis of individual effects from individual ETS compounds, as suggested by the commenter.

21. Comment: Page III-2: The statement: "….With few exceptions (e.g. hydrogen cyanide and organic acids), sidestream smoke contains greater mass emissions as compared to mainstream smoke (Jenkins *et al*., 2000) on a per cigarette basis…." requires some additional explanation. The reason why SS smoke contains more material typically is because greater mass of tobacco is consumed during smoldering, compared with active puffing.

Response: Staff agrees and has revised the draft report to show that more sidestream emissions occur due to greater tobacco mass consumption during smoldering.

22. Comment: Page III-3: In the top paragraph (Page III-3), the text fails to make clear that most of the mainstream smoke that contributes to ETS is exhaled mainstream, that has been diluted in the lungs of the smoker, aged, and scrubbed of some of its more soluble gas components.

Response: We agree with the commenter. The report has been revised to add clarity.

23. Comment: Page III-4, last paragraph: The monograph to which the citation Jenkins *et al.,* 2000 refers did not involve any new experimental work. No measurements were made.

Response: The commentor is correct that no new data was generated in the referenced work. Staff have revised the report to reflect this fact.

24. Comment: Page III-5, first paragraph: The statement "….In general, highly concentrated mainstream smoke has constituents preferentially distributed in the particle phase region (Jenkins *et al.,* 2000). Smaller sidestream smoke particles in the ambient air can be inhaled deeply into the lower respiratory tract, where they can have a deleterious health effect…." Suggests a nearly binary distribution of tobacco smoke droplets (particles) between SS and MS smoke. However, given the huge breadth of the distribution, the distribution of both smokes should be considered as continuums. Also, the suggestion that somehow the slightly smaller particle size distribution of SS may result in more deleterious health effects is not supported in the scientific literature. While there are many differences that are statistically different in the distribution parameters, such as the mass median aerodynamic diameter, it is not altogether clear that there is a true functional difference in the two distributions. If there is evidence of this, then the authors need to cite such.

Response: In developing the citation above, the staff recognized that ETS has a broad particle size distribution. While some scientific literature suggests that a continuum exists between mainstream and sidestream smoke, other researchers have found some differences with particle distribution. In figure III-3, staff show data from Morowska *et al.,* 1997 indicating that there exists an apparent difference in the number of ETS particles, which fall either into the submicron level, or the supermicron level indicating a binary distribution among these two aerodynamic sizes.

The second part of the comment takes issue with the statement indicating that smaller particles in sidestream smoke have more deleterious health effects. In general, it is well known that inhalation of fine particulate matter (i.e. PM10 and smaller) is more harmful than larger particles as the fine PM reaches deeper down in the lung.

25. Comment: "….there is little attempt to discuss the rationale of using outdoor air markers (such as the iso-alkanes or ante-isoalkanes) as long term markers for ETS in ambient air when many of the components of ETS have relatively short half lives outdoors. This apparent inconsistency needs to be addressed.

Response: Staff included a discussion of iso- and ante-iso alkanes (pg. V-6) as potential ETS markers. Staff noted that these markers are more stable in outdoor air and have characteristic concentration patterns associated with tobacco leaf combustion. In this section of the report, staff fully recognizes that there are several ETS markers that have been used by researchers, each with their own pros and cons.

26. Comment: Page VI-1: The statement "…..Alternatively, as ETS ages, semi-volatile constituents of ETS, such as nicotine, may shift from particulate phase to gaseous phase…." seems to be incongruent with the latest scientific evidence regarding the state of nicotine in ETS. Most nicotine in fact is in the vapor phase of ETS (mainly emanating from sidestream smoke) as the ETS begins to form. A much better example of the shift from particle phase to vapor phase would be neophytadiene or n-$C_{27}H_{56}$.

Response: The scientific literature supports the notion that particulate phase nicotine converts to gaseous nicotine. See response to comment #5. Staff recognizes that other ETS particulate components also convert to gaseous components and will also include neophytadiene as an example of this chemical phenomenon.

27. Comment: Page VI-2: The data reported in Table VI-1 presents a large range of atmospheric lifetimes for known constituents of ETS. The reported range is from 5 minutes to 12 days. Given this data, and the likely reactivity of many of the other constituents of interest, it seems very hard to make a case that what we refer to as "environmental tobacco smoke" is likely to maintain much of

its character after a few tens of minutes in the outdoor air. Given such, one would have expected for the Report to provide some rationale as to why it is reasonable to consider ETS wholistically as a toxic air contaminant….Without a clear ,strong justification as to why we should consider as some sort of single entity, when it is clearly not such, it would seem that the pollution which results from ETS best be considered on a constituent by constituent basis. Many of the compounds of interest are already regulated under a variety of regulations. No compelling evidence is provided for the case that ETS survives as an entity and should be considered as such.

Response: It is reasonable to consider ETS wholistically as a toxic air contaminant as it is emitted from a common source. The ARB has used this approach in the past when evaluating diesel exhaust as a toxic air contaminant. Diesel exhaust is also an example of a complex pollutant comprised of many individual compounds. Staff included data on the atmospheric persistence of individual ETS compounds because it is important to point out that the chemical nature of ETS has a temporal effect.

28. Comment: Data on indoor air from the 16 Cities Study (Jenkins *et al*., 1996) should be included in the report. In particular, data from Fresno, California should be included.

Response: Published data from the 16 Cities Study has been added to the report. However, neither the Jenkins *et al*. nor the Graves *et al*. published papers provide results specific for Fresno, California, and ARB does not have the staff available to obtain the data set and separate out the Fresno data. Because of the sample bias and lack of representativeness of the Jenkins *et al*. sample (discussed further below), particularly relative to California exposures as discussed in the Report, we do not believe such an effort to be worthwhile.

29. Comment: A) The commentor questions citation of Graves *et al.* instead of Jenkins *et al*., and also questions the statement that "…results are somewhat low relative to other similar studies…". B) Criticism of the demographic information presented in the Jenkins *et al.,* 1996 report is unjustified. The report fails to cite similar personal exposure studies and does not discuss the skewed demographics of other studies, such as Leaderer and Hammond (1991).

Response: A. Additional information from Jenkins *et al.* , 1996 has been added to the report. The results were viewed as somewhat low relative to other studies based on inspection of results of other studies of home nicotine measurements reported in Tables V-5 and V-6. For example, Guerin *et al.,* 1992 found that means across studies ranged from 1.6-21 ug/m^3 for homes with smoking, compared to a mean of 1.41 ug/m^3 in Jenkins *et al*., for individuals exposed away from work, but not at work.), and in Table V-6, Hammond (1999) showed a range of 1.5 to 5.8 ug/m^3, and Glasgow *et al.,* 1998 a mean of 6.3 ug/m^3 in homes with smoking during the monitoring period.

B. While the Jenkins *et al*. study is unique in obtaining a sample from cities across the United States, the representativeness and utility of that sample was compromised by the multiple selection criteria for participants reported in the Jenkins *et al.* paper. For example, several groups in several broad employment categories were excluded, and a criteria for 75% of time spent in their personal workspace was included; these and other restrictions on those selected for participation resulted in a study population that over-represented white females and white-collar workers, and under-represented blue collar workers, minorities, and some other groups, because of the nature of their jobs. Such extensive exclusion criteria are generally not found in scientific studies without serious reason. Most importantly, it is unclear how to apply the results of the study to the California population, because of our substantial non-Caucasian minority populations. Regarding the lack of similar discussion for other studies such as Leaderer and Hammond, as indicated throughout the report, we do not specifically discuss individual studies conducted prior to 1996 because those have been discussed previously in the documents cited in the report. We agree with the commentor that we do not cite any studies of ETS exposure that achieved a truly demographically representative sample of the U.S. population, because to our knowledge no such study has been conducted.

30. Comment: ARB failed to incorporate several important studies of nicotine and PM concentrations in smoking environments in Tables V-6 and V-8 (p. V-17, Table V-6, p. V-24). A list of citations was provided.

Response: Staff reviewed the studies cited in the comments. The 14 studies by Keith Phillips are international studies from Europe (e.g., Britain, Germany, Spain), Asia (e.g., Hong Kong, Beijing, Kuala Lampur), and the Pacific Islands (e.g., Australia). In these countries smoking behavior, cigarette formulation, housing characteristics, and non-smoker behavior may be very different than those in the United States and therefore would not be relevant to California indoor concentrations. Thus, they were not included in the report. Some of the Phillips work is used in the section on biomarkers.

Studies by Sterling *et al.*, 1996 and Jenkins *et al*., 2001 discuss smoking exposure in one or two office buildings in the eastern U.S. where smoking is prevalent and unrestricted. These and a number of other studies were not specifically included in the report because of the limited new information provided and the desire to focus on information most relevant to exposures in California, where unrestricted office building smoking is no longer permitted.

Two of the listed studies, Trout *et al.*, 1998 and Maskarinec *et al.*, 2000 discuss employee exposures to ETS in casinos, restaurants, and taverns. These results may be relevant to workers in California casinos, and so have been added to the report.

31. Comment: (p. V-23, and others) Unpublished data was cited from Repace (2003). There is concern that the method used over-reports the RSP concentration by a factor of 2.

Response*:* The work by Repace was published in September 2004 in the *Journal of Occupational and Environmental Medicine*. The appropriate citation has been added. In his paper, Repace discusses the fact that humidity and particle size effects oppose each other when measuring RSP with the MIE personal Data-RAM (pDR-1200: Thermo Electron Corporation). He also provides a figure to show comparability of his method with a model 3511 piezobalance.

A. Judson Wells, February 10, 2004

1. Comment: Page III-4 and 5: There has been too little attention paid in the U.S. to the work of Pritchard *et al*., Environ Technol Lett 1988; 9:545-552 …on what happens to aged, diluted ETS. They… found that, during aging and dilution, 70% of the particulate ETS tar evaporates into the vapor phase. Vapor phase tar, like other orgainic vapors (Bond et al. Toxicol Appl Parmacol 1985;78:259-267) would deposit quantitatively in the lung and the lung has no clearance mechanism for vapor phase deposits, whereas only about 15% of the particulates deposit on the lung, the remainder being exhaled. This phenomenon may explain why the passive risk is so similar to the active risk in non-contact sites like the heart and breast. It appears that the tar compounds that would evporate would have molecular weights in the 100 to 200 range which would include quinoline, ethyl quinoline, benzoquinoline, phenanthridene, nornicotine, beta-naphthyl amine, nitoroso pyrolidine, nitroso nornicotine, pyrene, fluoranthrene, phenol, the cresols, 2,4-dimethyl phenol, catechol, and the methyl catechols, all of which have some carcinogenic activity.

Response: Staff agrees with the commenter and have revised the report to include the findings of Pritchard *et al.,* 1988.

Maurice E. LeVois, Ph.D., March 25, 2004

1. Comment: 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 at least been 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 to such low concentrations that they are no longer quantifiable in ETS.

Response: As indicated by the references at the end of Appendix A, the list of known ETS constituents was taken from several studies which identified numerous compounds in ETS. The purpose of the list is to compile a list of known constituents that could be generated as tobacco products (i.e. cigars and cigarettes) are consumed. The staff did not present the list as all-inclusive and does not agree that the title is misleading. Furthermore, the compounds that are listed in both Table III-1 and Table III-2 represent those ETS components for which known health effects have been determined. The tables are shown to illustrate that several ETS constituents have been found to be harmful as individual compounds. However, the health effect evaluation conducted by OEHHA in Part B of the staff report do not distinguish between the health effects of individual compounds, but rather the effect of the total "mix" of compounds that make up ETS.

Robert F. Phalen, University of California, Irvine, March 1, 2004

1. Comment: Identification of ETS as a TAC will ultimately lead to more violence in bars and other establishments.

Response: If ETS meets the criteria for designation as a TAC, then it is the Board's responsibility to determine if it should be identified as one. This will occur only after a full public process which provides a full scientific debate of the issues. Furthermore, authoritative reviews over the past two decades have presented scientific evidence linking ETS exposures to a number of adverse health outcomes. These reviews were endorsed by organizations/agencies such as the U.S. Environmental Protection Agency, U.S. Department of Human Health Services, National Research Council, and the International Agency for Research on Cancer.

Further, no control measures are being proposed in this report. If a substance is identified as a TAC by the State ARB, it will enter into the control phase of the program. Any consideration of control measures will be made only after a thorough public process including public workshops, meetings with affected parties, and local air pollution control districts.

Peter N. Lee, P.N. Lee Statistics and Computing LTD., March 11, 2004

1. Comment: My paper is cited as P.N. Lee, 1999 ” when all the other references in the Draft do not give initials on page V-61. The reference on page V-78 is also not in its correct alphabetical order.

Response: We have corrected the citation to read Lee, 1999 and have put the reference in the correct order on page V-78.

II.

Office of Environmental Health Hazard Assessment Staff Responses to Comments on the Draft ETS Report Part B

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Comments received during or shortly after the Public comment period, with responses presented to the SRP on Tuesday, November 30, 2004

Comments received during or shortly after the Public comment period, with responses presented to the SRP on Tuesday, November 30, 2004:

Comments of the American Lung Association and the American Lung Association of California

Comment 1:

The American Lung Association is pleased to have the opportunity to comment on the draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, November 2003." First, we would like to applaud the California Air Resources Board (CARB) and the Office of Environmental Health Hazard Assessment (OEHHA) for their leadership and significant contributions to the scientific evidence regarding the detrimental health effects and harms of environmental tobacco smoke (ETS). This 2003 report builds on the scientific evidence outlined in the 1997 report, by updating the scientific understanding of the exposure and health impacts significantly. As a leading public health organization, the American Lung Association appreciates the volume of data that was collected and synthesized for the draft report.

A Toxic Air Contaminant is defined in Health and Safety Code section 39655 as: "an air pollutant which may cause or contribute to an increase in mortality, in serious illness, or which may pose a present or potential hazard to human health." The American Lung Association believes that based on the fact that there are more than 4000 chemicals in ETS, including 69 that are carcinogenic, the case is clear that ETS should be identified as a toxic air contaminant under California law.

While ETS is clearly linked to number of other health problems, the American Lung Association's comments will be limited to the impacts on respiratory health only. For over twenty years, the evidence has been building on the causal associations between environmental tobacco smoke and lung cancer and other respiratory effects. In 1982, the U.S. Surgeon General first raised concerns that toxins present in tobacco smoke might be causing lung cancer not only in those who smoke, but also in those who involuntarily breathe secondhand smoke. It stated, "although the currently available evidence is not sufficient to conclude that passive smoking causes lung cancer in nonsmokers, the evidence does raise concerns about a possible serious public health problem."

Scientific research into this concern led the U.S. Surgeon General to report compelling evidence in 1986, which was confirmed by research by the National Research Council and U.S. Environmental Protection Agency, concluding that ETS exposure does cause lung cancer and other respiratory outcomes. Much of the research reported in the Draft Report on ETS exposure and lung cancer amplifies and confirms what has been known and accepted for years. We commend the staff on the thorough compilation of new work that continues to strengthen this link.

Response:

Thank you for your comments.

Comment 2:

We would encourage the Science Advisory Panel to examine the methodology behind the attributed lung cancer deaths in your two reports. Currently the CDC and the 1997 Cal EPA report state that 3000 lung cancer deaths are attributed to ETS nationwide, which first appeared in U.S. EPA's 1993 analysis. We understand that this number may be outdated and underestimate the risk, but the attributable incidence and death estimates in the Draft Report are considerably higher. We understand that typographical and calculation errors on ES-11 and 7-76 that address this issue will be revised before the Science Advisory Panel reviews the next draft. More discussion of the methodology to reach both the California and national estimates is needed in the final report to justify this disparity and allow for comment. In order to be consistent, we would suggest using lung cancer deaths versus incidence as the point of comparison in Executive Summary Table ES2.

Response:

Thank you for pointing out these problems of which we were also aware. Errors in the original draft have been corrected. We have recalculated the attributable risk using the same methods that were utilized in the U.S. EPA 1992 estimates. These methods have undergone rigorous review and have been well accepted. The increase in risk noted in our new calculations comes largely from demographic changes during the interim. These calculations are spelled out in detail in the revised draft document.

Comment 3:

Another important topic reviewed in the Cal EPA report was the association of ETS with asthma exacerbations and induction. The American Lung Association is very interested in the scientific evidence that demonstrates linkages to asthma exacerbation, increases in asthma symptoms and induction of asthma from exposure to environmental tobacco smoke. We believe that the science is conclusive that ETS is a risk factor in the exacerbation of asthma in both children and adults. However, our review of the data in the Draft Report lead us to believe that the link to asthma induction in adults requires further scientific study to merit conclusive findings at this time. We encourage the Scientific Advisory Panel's investigation and comments on the staff report's recommendation to move from suggestive in the 1997 report to conclusive in this draft report regarding asthma induction in adults.

Response:

While we understand that good scientists and epidemiologists are appropriately reluctant to assign the term causative to an exposure without substantial and convincing evidence, we believe that indeed this hurdle has been cleared in the case of ETS and adult onset asthma. Some of the key factors are outlined below and our discussion has been expanded similarly in the revised document.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS

exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger et al. 1994), number of smokers in the environment (Leuenberger et al. 1994; Hu et al. 1997), duration of exposure to smoker (Leuenberger et al. 1994; Kunzli et al. 2000; Iribarren et al. 2001; Janson et al. 2001), duration of working with a smoker (Greer et al. 1993; McDonnell et al. 1999), measured nicotine levels (Eisner et al. 2001), and an ETS exposure index that incorporates both intensity and duration of exposure(Jaakkola et al. 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin 1995, Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999), or a defined period prior the development of asthma-like symptoms (Withers 1998, Strachan 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a causal association between ETS exposure and adult onset asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (California Environmental Protection Agency 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole et al. 1989),(Comstock et al. 1981),(Ng et al. 1993),(Masi et al. 1988),(O'Connor et al. 1987)-(Xu and Li 1995) (Schilling et al. 1977; Kauffmann et al. 1989) (Brunekreef et al. 1985)-(Abbey et al. 1998; Carey et al. 1999) (Jaakkola et al. 1995) (Dimich-Ward et al. 1998) (Eisner et al. 1998; Eisner 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of

ETS exposure and incident adult asthma (Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999, and Jaakkola 2003). Other studies have prospectively examined the relation between ETS exposure and incident wheezing (Withers 1998, Strachan1996). Fortunately, since the writing of the original draft of our document, a very useful paper has been published that provides the kind of evidence that has been difficult to obtain. This is a study in Finland by M. Jaakkola, et al (AJPH, 2003;93:2055-2060), which was a large population based incident case-control design in a system that had the advantage of being able to define all incident cases of new onset asthma diagnosis. Diagnosis was based on clinical examination and included lung function measurement. Recruitment was aided by being able to identify via National Social Insurance records all patients who had received reimbursement for asthma medications and included 521 newly diagnosed case patients out of a population of over 440,000. The risk of new onset asthma in adults age 21-63 was doubled in those exposed to workplace ETS (OR 2.16, CI 1.26, 3.72) and nearly five fold in those with home exposure (OR 4.77, CI 1.29-17.7). Cumulative exposure over a lifetime at work and at home increased risk. This study indicates that cumulative lifetime exposure to ETS increases the risk of adult-onset asthma. A summary of this paper is included in the revised document.

The population-based study by Jaakkola and colleagues provides the strongest evidence to date that links ETS exposure to incident adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of incident adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

Comment 4:

The issue of asthma induction in children is more complex. There is no doubt that higher rates of asthma exist in children of smoking parents. Prenatal exposure from a smoking mother does appear to alter lung growth and development *in utero* as the inhaled tobacco crosses the placenta. This would suggest a causal relationship between prenatal maternal smoking and asthma induction in children. Many of the studies in the Draft Report do not seem to distinguish between pre- and postnatal exposure. While the Lung Association supports the conclusive link of asthma induction in children, we would welcome a more robust examination of data that differentiates between pre- and postnatal exposure. It is very difficult to prove causal damage and the research is not as clear as to whether postnatal ETS exposure triggers an attack in a child who is predisposed to asthma or induces the first asthma attack of an existing condition. (Given the suggestive link between paternal smoking preconception and childhood cancers, this might also be another area of research to pursue in relation to childhood asthma induction in non-smoking mothers as well.)

Response:

The current document "Health Effects of Environmental Tobacco Smoke" is not intended as a stand-alone volume but rather as additional information to update the 1997 document (see Section 1.0, chapter1, part B). The issue of induction of childhood asthma was dealt with in the 1997 volume and the conclusion that ETS exposure causes induction of childhood asthma was supported by the review by the Scientific Review Panel. The additional evidence presented in this update is supportive of the previous findings. The paragraph below summarizes the previous conclusion, which in part was based upon a meta-analysis performed by OEHHA and included in the 1997 document:

> *"*There appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (*e.g.,* Martinez *et al.* 1992). This finding suggests that a threshold of ETS exposure intensity is required in order to evoke this response. The temporal relation between childhood asthma and parental smoking is not at issue here, since asthma in children is unlikely to precede active smoking by their parents. However, it might be argued that, since the association seems to be strongest between maternal smoking and asthma prevalence in pre-school children, the key exposures may have taken place *in utero*. Several recent studies suggest that pre-natal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994, 1995, Hanrahan *et al.* 1992). It is possible that pre-natal effects may play a role as well in the etiology of childhood asthma. However, the studies by Chen (1986, 1988, 1989), showing effects of paternal smoking alone, as well as studies of ETS exposure linked to increased risks of asthma in nonsmoking adults (Leuenberger *et al.,* 1994), indicate that post-natal exposures can be sufficient to elicit this outcome. Development of asthma as a result of ETS exposure is "coherent" with other investigations demonstrating that both active and passive exposure to cigarette smoke are associated with increases in airway responsiveness, which (as noted above) is a characteristic feature of asthma. The biological plausibility of this relationship is strong: (1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; (2) ETS causes airway hyperresponsiveness; (3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; (4) cigarette smoke causes airway inflammation in active smokers (Niewohner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling."

There appears in the literature both evidence of an increase in incidence of asthma in children whose mothers smoked during pregnancy and then had additional exposure postnatally (over those not postnatally exposed) and in children who were not exposed to maternal smoking in utero but were exposed only postnatally. To address the request for further evaluation of this data we are including a meta-analysis conducted by OEHHA (updated from the 35 studies reviewed in the 1997 document to include 85 studies) of the literature in the final draft. The table below from this new analysis summarizes the four studies in which a statistically significant

increase in asthma was found in children who had only postnatal exposure and for whom the studies controlled for child's allergies or a family history of allergy and child's own smoking.

Table 1: Studies that examined postnatal ETS exposure and found a statistically significant relationship between postnatal exposures to ETS only and the development of asthma in children

Study	Design	post natal only	lcl	ucl	both	lcl	ucl	ages	Exposure measure	issue
Agabiti Current asthma	Nested case control	1.25	1.03	1.52	1.83	1.19	2.80	6-7	Mother was ex smoker	Ex smoker
Azizi 1995 current asthma	Case control	1.91	1.13	3.21	----	----	----	1m - 5	No mothers smoked, others smoked in the same bedroom as child	Others smoked in same bedroom
Neuspiel wheezy bronch.	Prospective cohort	2.16	1.19	3.93	1.52	1.27	1.82	0-10	Lifetime exposure	Lifetime exposure
Mannino Current asthma	Cross sectional	4.4	1.40	13.5	7.3	2.5	21.2	4-6	highest tertile of cotinine	Younger child high exposure

Other metrics within some of these studies as well as other studies that also controlled for these important factors do not show a statistically significant association and are summarized in the table 2 below.

We feel that the discrepancies between the findings in these two tables are understandable and that several factors have been identified by the authors of the cited studies themselves that explain why some observe effects and others do not. In general, those studies that were able to identify higher (Mannino, Azizi) and longer exposures (Mannino, Neuspiel) identified significant associations. High exposure categories (by history or cotinine) and lifetime exposure are less prone to misclassification. Also, significant findings may be more difficult to identify in older children when their exposure is defined as "current ETS exposure" as it is in many studies. Current smoking habits are much more likely to reflect the smoking habits of mothers in early childhood but may misclassify the early childhood exposures to ETS in older children (i.e. mothers that quit during pregnancy may have started smoking again later in their child's life) (Mannino, Agabitti).

Table 2: Studies that examined postnatal ETS exposure but did not find a statistically significant relationship between postnatal exposures to ETS only and the development of asthma in children.

Study	Design	post natal only	lcl	ucl	both	lcl	ucl	ages	Exposure measure	issue
Mannino Ever asthma	Cross sectional	0.8	0.30	2.1	0.7	0.3	1.7	7-11	highest tertile of cotinine	Ever asthma, older child
Mannino Current asthma	Cross sectional	0.9	0.40	2.5	0.6	0.2	1.7	7-11	highest tertile of cotinine	Older child
Ehrlich 1996 Current asthma/wheeze	Nested case control	0.8	0.45	1.44				7-9	Mother current smoker, cotinine levels in child more closely associated with # of HH smokers	Few mothers smoked more than 10 cigs/d Older child
Agabiti Current asthma	Nested case control	1.02	0.85	1.21	0.69	0.45	1.06	13-14	Mother was ex smoker	Older child
Mannino Ever asthma	Cross sectional	2.2	0.90	5.0	4.4	1.4	13.5	4-6	highest tertile of cotinine	Ever asthma
Agabiti Current asthma	Nested case control	1.12	0.93	1.35	1.62	1.34	1.96	6-7	Mother was current smoker	Older child
Agabiti Current asthma	Nested case control	1.15	0.99	1.34	1.22	1.02	1.47	13-14	Mother was current smoker	Older child

We feel that it is a semantic issue as to whether a child who has been exposed in utero and then develops asthma after postnatal ETS exposure can be said to have ETS induced asthma or an uncovering of a pre-existing tendency. Even though postnatal exposure leads to an increased risk among those already primed by prenatal exposure, we would still consider the onset of asthma as induction by ETS.

Below are data from Dr. Mannino's paper (Arch Pediatr Adolesc Med, 2001) that are displayed as his figure 1 in that publication. In this he has clearly separated out children with high continine who were and were not exposed to maternal prenatal smoking (PNS). In the younger age grouping of 4-6 years there is a clear and significant increase in risk of current asthma comparing the highest cotinine tertile with lowest without exposure to PNS. This is exacerbated in those with PNS. For ever asthma, there is an elevated but not statistically significant risk noted. These were not seen in the older ages but as noted above this may be a reflection of

current cotinine levels being more reflective of lifetime exposure in early childhood than in later years.

Children 4-6	*N*	*Ever Asthma*	*Current Asthma*
Hi Cot + PNS	248	3.1 (1.1 - 8.8)	7.3 (2.5, 21.2)
Hi Cot - PNS	375	2.2 (0.9, 5.0)	4.4 (1.4, 13.5)
Mod Cot + PNS	51	1.7 (0.2, 17.6)	5.2 (0.6, 47.6)
Mod Cot - PNS	539	0.6 (0.3, 1.3)	0.9 (0.3, 2.4)
Low Cot + PNS	19	2.6 (0.3, 24.0)	1.7 (0.3, 11.1)
Low Cot - PNS	388	1	1

A more complete discussion of the above analysis will be included in our final draft under "child/asthma induction meta-analysis".

Comment 5:

It is becoming increasingly clear that environmental tobacco smoke is a serious toxic air contaminant, affecting the health of millions of Americans. We must continue to respond to the science with aggressive policy and legislation in order to lessen the impact of this deadly substance. We thank the State of California for expending the resources to update the scientific research associated with Environmental Tobacco Smoke and move that it finalize the report as a first step in strengthening protections from ETS.

Response:

Thank you for your review and comments.

Comments of R. C. Burton of the National Cancer Control Initiative (Australia)

Comment:

I have a long standing interest in a possible causal relationship between active and passive exposure to cigarette smoke and breast cancer. My most recent publication was:
Burton R C, Sulaiman N. Cigarette smoking and breast cancer, is a real risk emerging? Medical Journal of Australia 2000; 172:550-552.
In that review I concluded that a causal association had not been established but was both biologically and epidemiologically plausible and likely.

I have read carefully and with interest the relevant pages on breast cancer and cigarette smoke exposure contained in the first 11 pages of Chapter 7 and pages 7-91 and 7-155 of the proposed revision to your 1997 report, which I obtained from the web address:
htti)://www.arb.ca.qov/toxics/ets/dreport/dreDort.htm.

I agree with the conclusion that the totality of findings now provides evidence of a causative association between both active cigarette smoking and exposure to environmental tobacco smoke and breast cancer. The studies published since I reviewed the literature are of high quality, and taken together with the older literature support the conclusion that has been reached in that report.

In particular, the risks associated with cigarette smoke exposure when the breast is undergoing rapid cell division should be emphasized. That is, during childhood through puberty and in first pregnancy. I would be pleased to provide further commentary should you require it.

Response:

Thank you for your comments.

Comments of Wade S. Brynelson
Assistant Superintendent, Learning Support and Partnerships Division, California Department of Education

Comment:

Thank you for providing the California Department of Education (CDE) the opportunity to comment on the California Air Resources Board's draft report "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003." This document clearly shows the many causal links between environmental tobacco smoke (ETS) and health issues. Some of these issues are currently addressed in California's public schools as a result of Proposition 99, The Tobacco Tax Initiative.

With the passage of Proposition 99 in 1988, California public school districts have been required to implement tobacco-free school policies as a condition of receiving funds for tobacco-use prevention education (TUPE) and intervention programs in schools. This policy prohibits the use of tobacco products by students, staff, and visitors, at any time, in district-owned or leased buildings, on district property, and in district vehicles. As a result of this policy, approximately 95 percent of all California public schools have effectively eliminated ETS on district property. Schools are also required to present tobacco-use prevention lessons that include a discussion of ETS and its effects on the human body.

In addition, districts receiving TUPE funds are required to provide individualized counseling and advocacy services to all pregnant minors and minor parents regarding perinatal and postnatal tobacco use. The release of studies, including those cited in your report, are making school nurses and other school staff aware of the relationship between ETS and its adverse effects on the fetus, newborn, and older children.

I commend you and your staff for the thorough and unbiased examination of the many studies that have been conducted regarding ETS risks. The approval of this report will provide further corroboration of the need for existing and proposed policies that protect children and adults from the health risks associated with exposure to ETS. The health of children in particular has a great impact on their success in school as they cannot learn if they are home ill or not at their best in the classroom.

Response:

Thank you for your comments.

Comments of Dennis Eckhart, Senior Assistant Attorney General, Tobacco Litigation & Enforcement Section, State of California Attorney General's Office

Comment:

Thank you for the opportunity to provide comments on the draft report, Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. The Tobacco Litigation and Enforcement Section of the Office of the California Attorney General is responsible for ensuring compliance with the Tobacco Master Settlement Agreement. The Attorney General's Office has focused on a number of issues concerning the health effects associated with exposure to environmental tobacco smoke. The report's summaries of the latest scientific research regarding environmental tobacco smoke, and Cal EPA's conclusions based upon these studies, will be extremely valuable to our continued enforcement efforts.

The agency is to be commended for compiling and analyzing all of the research contained in the report. The report provides a thorough and balanced review of the scientific literature on secondhand smoke, including the large number of studies that have been published since the release of Cal EPA's 1997 report on secondhand smoke.

As a law enforcement agency, the Attorney General's office appreciates the basic explanation of the medical terminology and illnesses discussed in the report. Providing definitions and background information on illnesses associated with ETS exposure is a significant aid in understanding the studies and clinical trials reviewed in the report.

The detailed descriptions of the particular studies, including their research methodology, findings, and possible confounding variables and other concerns, is very useful for examining individual studies that may be of special interest, and for reviewing the basis for the conclusions in the report. Further, collecting all of these studies in a single volume greatly simplifies the task of researching studies on ETS exposure.

We look forward to Cal EPA's continued examination of the health effects associated with exposure to environmental tobacco smoke.

Response:

Thank you for your comments.

Comments of Diane J. Fink, MD, Chief Mission Delivery Officer, Americal Cancer Society, California Division

Comment:

On behalf of the American Cancer Society, California Division, we are writing in strong support of the California Air Resources Board's proposal to identify environmental tobacco smoke (ETS) as a toxic air contaminant.

The scientific evidence demonstrating the health hazards of ETS has been overwhelming for years. ETS has been classified by the U.S. Environmental Protection Agency as a Group A carcinogen. Group A carcinogens include only the most dangerous substances such as asbestos and radon. ETS contains over 4,000 substances, more than 40 of which are known or suspected to cause cancer in humans and animals. Each year, about 3,000 nonsmoking adults die of lung cancer as a result of breathing ETS.

Enclosed for your reference is the American Cancer Society's Cancer Facts & Figures 2003. In addition, may we refer you to your colleagues in the California Department of Health Services, Prevention Section, Chronic Disease & Injury Control Branch, Tobacco Control Section. They possess a wealth of exposure and other ETS data more recent than the 1999 data cited in your report.

We believe that ETS, a proven air-borne carcinogen, should be classified as a toxic air contaminant. The evidence is unequivocal.

Response:

Thank you very much for your additional information and your comments.

Comments of Jennifer Jinot, U.S. Environmental Protection Agency.

Comment 1:

It's not clear from table 1.2 or from the text in chapter 1 (e.g., 2nd sentence of 3rd paragraph of section 1.0: "Table 1.2 presents estimates of impacts form some of the health effects associated with ETS exposure, and predictions of the numbers of *people* potentially affected in California,..." [emphasis added]) what the target population of the assessment is. I assume that it is nonsmokers, but active smokers are also affected by ETS. And how are nonsmokers defined? Are the population risk estimates for never-smokers only, or do they include long-term former smokers?

Response:

The definition of nonsmoker is somewhat study-dependent and ranges from never smoked at all to never regularly smoked more than 100 cigarettes in the subject's lifetime, to not smoking in the previous two weeks. For the endpoints associated with pregnancy, LBW and PTD, and for cardiac death and lung cancer death, the target populations are nonsmokers. Ex-smokers are not excluded. Estimates for the childhood endpoints, asthma, otitis media and SIDS, include only never-smokers. We have clarified this in the text.

Comment 2:

Also in Table 1.2, the attributable risk estimates are presented with too many significant figures. This gives an undue impression of greater precision than there really is.

Response:

Those estimates have been rounded to better reflect their precision.

Comment 3:

With respect to the actual estimates in Table 1.2, I found the derivations of the OM and SIDS estimates, but I wasn't able to find the derivations of the LBW, PTD, or asthma estimates. If they're not in the assessment, they probably should be, because people are going to be citing the estimates, and some folks will want to know how they were derived.

Response:

The text has been amended to show how the estimates in Table 1.2 were derived. PTD has been deleted since we only present estimates for the health effects we consider causal.

Comment 4:

On page 1-10, in the paragraph immediately above Table 1.2, the 3rd sentence doesn't really follow from the 2nd. I think that the intention of the paragraph is to say something more like:

> "With regard to addressing biological plausibility for ETS effects based on active smoking data, analyses based on particular biomarkers should be considered with caution. Presumption of a linear dose-response between an effect and tobacco smoke exposure from either active smoking or ETS exposure as indicated by biomarker measurements ~~and effect~~ can be problematic. The ratios of constituents in mainstream smoke and ETS differ~~s~~, ..."

Response:

The commentator's suggested wording adds clarity and has been incorporated.

Comment 5:

Finally, in the references to chap. 1, there is a Taylor and Tweedie (1997) reference that says it's "in press". surely, that's been published by now if it's ever going to be?

Response:

The references have been amended to reflect the study's publication in Environmetrics 8(4): 351-372.

Comment 6:

It seems that subsections 3.1.2 and 3.1.3, which have to do with ETS *exposure* assessment, should be in their own section rather than part of Section 3.1, which is on mechanisms of injury.

Response:

Thank you for your suggestions; however, we note that there is an entire second document on exposure assessment so we have left the organization as is..

Comment 7:

At the beginning of Section 3.2.1, it would be helpful to have standard definitions for some of those effects, i.e., LBW, SGA, etc.

Response:

These definitions have been added.

Comment 8:

Some of the entries in Table 3.1 aren't consistent in reporting the "n"s for nonsmokers, but the results presented are for nonsmokers, so it would be helpful to have all the numbers consistently referring to nonsmokers.

e.g., Ahluwalia et la. n=13,497 for nonsmokers according to the text

Response:

Table 3.1 has been modified to indicate the "n" for non-smokers where appropriate.

Comment 9:

Also some of the "n"s aren't consistent across the various tables and text in chapter 3. I know that sometimes the original n isn't the same as the n with all the data necessary for analysis, but unless it's explained in the text what the various n's correspond to, the document should consistently use just the most relevant value.

E.g., for Dejmek et al., Table 3.1 reports n=8,624, but the text (p. 3-30) and Table 3.3 refer to 6,866 mother-infant pairs without any reference to an n of 8624, and of these, 4,309 were reportedly nonsmokers prior to conception. but then Table 3.3 refers to 3710 + 1797 maternal nonsmokers (w/ and w/o ETS), which adds up to 5507, which is close to the 4309 + the smokers who quit in the 1st and 2nd trimester (734 + 467) = 5510. but none of this is clear. and the results presented in Table 3.1 are for the nonsmokers specifically, not for n=8624 or n=6866.

Response:

The numbers reported in the tables and text have been verified with the original papers and the inconsistencies eliminated. Where it adds clarity, labels have been added to identify to what the "n" refers.

Comment 10:

In the Jedrychowski & Flak study, I got the impression that the cotinine levels were just used for the validation part of the study. So the results presented in Table 3.1 are for self-reported exposure, right? So I would omit the comment that the cotinine cutoff would mix light and non-smokers, because it makes it appear as if that mixing would be reflected in the reported results, but i don't think that's correct.

Response:

OEHHA agrees with the commentator's interpretation and the text mentioning the cotinine cutoff has been removed from the table.

Comment 11:

Also, on page 3-15 about the validation part of the study, the cutoff was used to separate smokers and nonsmokers, so the sentence "Nevertheless, based on the 25 ng/mL criterion, the authors found a significant misclassification (false negative) rate of 57% of ETS-exposed women as non-exposed" didn't make sense to me.

Response:

The commentator's confusion is understandable as the authors used a non-standard definition of misclassification. The text has been reworded and expanded as follows to add clarity. "Nevertheless, based on the 25 ng/ml criterion, the authors found a significant misclassification (false negative) rate of 57% reflecting women with plasma cotinine >25 ng/ml who claimed to be never or ex-smokers. Among the 142 women claiming to be never or ex-smokers, 5.6% had plasma cotinine above 25 ng/ml. Adjustment of the ORs for misclassification would raise the risk estimates."

Comment 12:

With respect to the Kukla et al. study, the text (p.3-28) says that babies of mothers passively exposed to > 15 CPD had a mean BW 49 g lighter, but Tables 3.1 and 3.3 say the decrease was 74 g. Also there appears to be a typo in Table 3.3 - according to the text and Table 3.1 MNS w/ETS should be 1178 not 1378.

Response:

The BW decrement in the text (49 g) is correct and the tables have been corrected. 1178 is the correct number and the table has been changed.

Comment 13:

In the first sentence of the discussion of Windham et al. (1999) on p. 3-22, i believe that it should read "992 *non*-smokers" not "992 smokers".

Response:

The commentator is correct and the text has been changed.

Comment 14:

2nd-to-last sentence on p. 3-29: I believe that should read "mothers' cotinine levels were above 1 ng/mL, ..."

Response:

The commentator is correct, however, that study has been replaced with a newer one by the same group.

Comment 15:

On p. 3-43, 4th sentence on Chatenoud et al. study: i think that should be: "The OR for SAB associated with ~~parental~~ paternal smoking..."

Response:

The commentator is correct and the text has been changed.

Comment 16:

p. 3-48, 2nd sentence: "But... the risk of a cleft for a fetus of a maternal non-smoker was similar to that of babies who carry the A2 allele and ~~maternal smokers~~ whose mothers were smokers ~~babies carry the A2 allele~~."

Response:

The commentator's suggested wording is clearer and has been incorporated.

Comment 17:

p. 4-24, section 4.3.2, 2nd sentence: "However ... children persistently exposed to ~~passive smoke~~ ETS..." [exposure can be passive but not the smoke] similarly, on p. 4-25, 1st sentence of Dollberg et al. discussion, and first line of p. 4-26.

Response:

Good point. The text has been changed.

Comment 18:

The conclusions on asthma induction in children and on asthma induction and exacerbation in adults in this draft are stronger than those in the 2000 National Academy of Sciences report on asthma. i would like to see some discussion of how the current evidence or CalEPA's interpretation of the evidence are different from that 2000 report.

Response:

Regarding the health impacts of ETS exposure on asthma, the National Academy of Sciences concluded in their 2000 report on asthma (NAS, 2000) that the evidence indicates a causal

relationship between ETS exposure and asthma exacerbation in preschool-aged children. OEHHA agrees with this assessment.

The report further stated that there is an association between ETS exposure and the development of asthma in younger children but it stopped short of claiming that the association is causal.

Based on several studies, many of which have been published since the NAS report, OEHHA finds that the evidence does support a causal association between ETS and asthma induction in children. Among children examined in NHANES-III by Gergen et al. (1998) and Mannino et al. (2001), the highest risk for asthma was associated with the highest ETS exposures. The study by Mannino et al. was noteworthy in that ETS exposure levels were biochemically verified by serum cotinine measures, the highest of which were associated with the greatest risk for ever or current asthma.

For older children and adults, the NAS report concluded that there is limited or suggestive evidence of an association between chronic ETS exposure and exacerbations of asthma. Regarding the development of asthma in school-aged children, the report concluded that the data are insufficient to establish an association with ETS exposure. As mentioned in this update, there is no "gold standard" for defining asthma in epidemiological research. However, as indicated by Toren et al. (1993), respondents' reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma than reliance strictly on self-reported asthma. Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney et al., 1989). Several studies described in this update found an association between ETS exposure and asthma or wheezing in adolescents (Withers et al. 1998) and in adults (Hu et al., 1997b; Irabarren et al., 2001; Janson et al., 2001; Kunzli et al., 2000; McDonnell et al., 1999). Collectively these studies support a causal association of asthma with chronic ETS exposure.

Comment 19:

I found the discussion of ETS and cystic fibrosis in CalEPA's 1997 ETS report very interesting. I didn't find cystic fibrosis mentioned in this draft at all. Is there no new evidence one way or the other on ETS and cystic fibrosis?

Response:

Two new studies have been summarized and added to the document. A small study by Beydon et al. (2002) found that ETS exposure exacerbates airway occlusion in children with cystic fibrosis. A larger study by Smyth et al (2001) found no effect of ETS exposure on lung function among children with cystic fibrosis. These new studies do not alter the original conclusion that the effects of ETS in cystic fibrosis are uncertain.

Comment 20:

In Section 6.2.3. it seemed that there were several new studies with strong evidence on lung development in children. I would have expected the updated findings (e.g., Table 6.00) to at least be "Suggestive (strengthened)".

Response:

Upon reflection, OEHHA agrees. The table has been changed.

Comment 21:

In Table 6.01, p. 6-4, re: the Li et al. study. the comments say that "In utero exposure strongly associated with decreased pulmonary function *especially if combined with postnatal ETS ...* [emphasis added]". However, most of the decreases in function listed seem to be of *lower* magnitude for "in utero + postnatal" vs. for "in utero" alone.

Response:

The sentence in question referred to FEV1 measures in boys. The table has been modified to clarify this.

Comment 22:

In Table 6.03, p. 6-15, under the Jindal et al. findings, it should read "1.7 vs. 6.1 p<0.01", i.e., the "1.7" is missing.

Response:

The 1.7 has been re-inserted.

Comment 23:

In Table 6.04, p. 6-20, under Li et al. outcome, where it says "overall", the presented OR is for hospitalizations. it appears, though, that it is overall across the age groups since listed below are different age groups, but the age group ORs are for LRIs and the "overall" OR is for hospitalizations.

Response:

The commenter is correct and the table has been altered to clarify this point.

Comment 24:

In Table 6.04, p. 6-22, under Peters et al. study description, it says "1.5 - 13 yr-olds"; however, in the text (p. 6-31) it says that the 10,402 children are "ages 8 - 13 years".

Response:

The text is correct and the table has been changed.

Comment 25:

In Table 6.12, p. 6-49, under Willes et al. exposure, the "15" in "15 ppm" got split across two lines.

Response:

They have been re-united

Comment 26:

In Table 6.13, p. 6-57, under Mannino et al. study description, it specifies 4-6 yr olds, and the results are the results for 4-6 y.o.'s, but the N = 13,944 isn't just for the 4-6 y.o.'s, so it could be confusing the way it's presented.

Response:

The number 13,944 includes all children in the study. The numbers for each age group, including 4-6 y.o, have been added to the table.

Comment 27:

In Table 6.13, p. 6-57, under Gergen et al. study description, the "2" is missing from "2 mo. - 5 yr"

Response:

The "2" has been added.

Comment 28:

In Table 6.13, p. 6-59, under Beckett et al. study description, it says "< 19 yr", but in the text (p. 6-67) it says "less than 18 years"

Response:

The text is correct and the table has been changed.

Comment 29:

On p. 6-88, in Table 6.17, under Jaakola et al. study description, it says "18-40 yr old" but in the text on same page its says "aged 15-40".

Response:

The text is correct and the table has been changed.

Comment 30:

On p. 6-89, the 3rd paragraph begins "*Dubus et al. (1998)*". I think that that should be Abbey et al.

Response:

The commentator is correct and the text has been changed.

Comment 31:

On p. 6-90, the 2nd paragraph begins "Emmons et al. (1996)". I think that that one should be Berglund et al. (1999).

Response:

The commentator is correct and the text has been changed

References used in responses:

Beydon N, Amsallem F, Bellet M, Boule M, Chaussain M, Denjean A, et al. (2002). Pulmonary function tests in preschool children with cystic fibrosis. Am J Respir Crit Care Med 166(8):1099-104.

Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, et al. (1989). Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. Eur Respir J 2(10):940-5.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD (1998). The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. Pediatrics 101(2):E8.

Hu FB, Persky V, Flay BR, Zelli A, Cooksey J, Richardson J (1997b). Prevalence of asthma and wheezing in public schoolchildren: association with maternal smoking during pregnancy. Ann Allergy Asthma Immunol 79(1):80-4.

Iribarren C, Friedman GD, Klatsky AL, Eisner MD (2001). Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 55(10):721-8.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358(9299):2103-9.

Kunzli N, Schwartz J, Stutz EZ, Ackermann-Liebrich U, Leuenberger P (2000). Association of environmental tobacco smoke at work and forced expiratory lung function among never smoking asthmatics and non- asthmatics. The SAPALDIA-Team. Swiss Study on Air Pollution and Lung Disease in Adults. Soz Praventivmed 45(5):208-17.

Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J (2001). Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med 155(1):36-41.

McDonnell WF, Abbey DE, Nishino N, Lebowitz MD (1999). Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. Environ Res 80(2 Pt 1):110-21.

NAS (2000). Exposure to Environmental Tobacco Smoke. Clearing the air: asthma and indoor air exposures (2000). Washington , DC: National Academy Press, p. 263-97.

Smyth A, O'Hea U, Feyerabend C, Lewis S, Smyth R (2001). Trends in passive smoking in cystic fibrosis, 1993-1998. Pediatr Pulmonol 31(2):133-7.

Toren K, Brisman J, Jarvholm B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. Chest 104(2):600-8.

Withers NJ, Low L, Holgate ST, Clough JB (1998). The natural history of respiratory symptoms in a cohort of adolescents. Am J Respir Crit Care Med 158(2):352-7.

Comments of Kenneth G. Brown PhD. of KBinc, Chapel Hill, North Carolina

Comment:

Re: Comments on "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" A draft report from the California Air Resources Board

I have primarily focused on Section 7.4.1, Breast Cancer. It is obviously difficult to evaluate and compare results from such a wide variety of studies, and you have done a very commendable job.

My comments are in reference to Tables 7.4F and 7.4G, entitled "Summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure" and "Summary risk estimates for ETS and premenopausal breast cancer", respectively. Summarizing the relative risks and confidence intervals by categories of "likely" and "unlikely" missed-important-ETS-exposure is illuminating, suggesting a sensitivity of outcomes to the thoroughness of exposure assessment. Although I think you have used the best single approach, you may be interested in adding results from another approach that is less powerful but is complementary in the sense that it makes different assumptions.

If the studies within a table are independent, and the observed values of RR (odds ratio or relative risk) are equally likely to be too large or too small, then under the null hypothesis RR = 1, the number of observations (S) in which the observed RR exceeds 1 is binomially distributed with parameters N (the number of studies) and P (the probability of an observed value of RR greater than 1). Against the alternative hypothesis that RR > 1 (a breast cancer increase), the null hypothesis is rejected for large values of S. The significance level is the probability that the value of S, or larger, would occur by chance if the null hypothesis is true.

Table	ETS Expos. Missed	N	S	Significance level
7.4F	likely	10	7	0.17 NS
7.4G	likely	5	5	0.03 S
7.4F	unlikely	5	5	0.03 S
7.4G	unlikely	5	5	0.03 S

Now consider the same approach, except that S is the number of studies in which the lower confidence bound exceeds 1, which means that the null hypothesis (RR = 1) would be rejected for those studies individually against the alternative that RR > 1 with significance level 0.025 or lower (which occurs because the test is one-sided and the confidence intervals are 95%). The assumptions are modified accordingly.

Table	ETS Expos. Missed	N	S	Significance level	
7.4F	likely	10	1	0.22	NS
7.4G	likely	5	1	0.12	NS
7.4F	unlikely	5	5	0.0000	S
7.4G	unlikely	5	5	0.0000	S

The studies for "unlikely" are consistently significant (5 of 5) with rejecting the hypothesis RR = 1 in favor of RR > 1, at the 0.025 level, while the outcomes for the "likely" studies are mixed. It should be noted that the same five studies are "unlikely" in both tables. If these studies are qualitatively better in the sense of having better exposure assessment, they might also be better in other characteristics that could be contributing to the difference in the outcomes.

Response:

Thank you for this sharing this interesting alternative approach to the analysis. Your analysis is supported by the test for homogeneity among the two groupings. In the test for homogeneity, studies with better exposure assessment appear to be a homogeneous group.

Comments of Charles Klivans, Dennison TX

Comment:

I am not a health professional, but in fact a retired Mechanical Engineer who specialized in a career dedicated to command and control hardware and software development on such programs as the Saturn Five Second stage checkout, and most recently, before retirement, I was the Aerospace Corporation responsible engineer for verification of the Global Positioning System (GPS) hardware and software as required by contract to the U.S. Air Force, from 1976 through 1993 when I retired after success rewarded by our team's winning the Collier Trophy in 1993. When my wife had a stroke, in 1993,1 retired at age 68.

My experience with ETS starts with free cigarettes in the U.S. Navy in 1945 and the unusual result that I became a lifelong non-smoker. I was neither addicted to or an admirer of smoking. I couldn't stand the things. I gave my smoking friends all my cigarettes. My first wife was a smoker and we were married for 47 years. She smoked regularly (2 packs a day) and died of Colon Cancer in Jan. 2002, with all doctors agreeing that smoking had nothing to do with her Colon Cancer. I was exposed to ETS through both courtship and marriage for 56 years. I recently re-married to another smoker, so I have been exposed to ETS for 57 years. When is it going to cause some disease that will kill me? I'm now 79 and ETS has had no effect on me. If it shortens my life, I will still have lived longer than the average predicted by the Surgeon General (SG).

My background to comment on ETS is based on my reading as many SG reports as 1 could find, the text "Foundations of Epidemiology", the Program Description Document of SAMMEC, the program that is used to determine the "risk" of smoking, and a text by Steven J. Milloy (Science Without Sense" which de-bunks the EPA effort to use "Risk" as means of damning smoking. I have studied the difference in "proof " of cause as determined by Engineeering's Scientific Method, and "Risk" as indicating cause by medically favored Epidemiology. It is like Apples and Oranges, where "risk" is a mathematical simulation, and "cause" is the result of physical testing, not simulation. Steven Milloy's book has a Table that shows the "Risk" of ETS as 1.13, a value lower than the "Risk" of sudden heart attack from 3 cups of coffee a week! While the Tome "Foundations of Epidemiology" states that Biological Credibility must support the Epidemiological findings (I cannot find ANY biological credibility to ETS as a report that proves ETS kills anything) it still leaves the door open if the "Risk" exceeds 3.0. But there is no Biological credibility to the claim ETS is a threat unless you consider the off-hand comment so often used that "ETS has 4,000 chemicals in it" some of which are known poisons. But the amount required of any of these chemicals to be dangerous is not mentioned, (the threat of poison is in the dose) and the amount produced is also not shown. The current value of (Risk) of 1.13 was reached by the EPA who was chastized in court for the method they used to even get that miniscule value by a judge Osteen. Careful review of the 34 "studies" making up the basis for the risk of ETS reveals two of the "studies" "Risk" value show ETS is GOOD for you! (less than 1.0). There is NO RISK to ETS. This was recognized until about 1980 when it became "unfashionable" to admit there is not only no scientific evidence, but also no risk from second

hand smoke. An actual test report in 1972 shows that worst case, ETS totals 2 dozen cigarettes a year!.

The real problem with ETS is that no one worries about "cause" any more because Epidemiological studies to determine "risk" are used instead of tests to find cause. That is why with all the hoopla about restricting smoking and de-toxing cigarettes, the American Cancer Society presents reports every year that estimate an increase in lung Cancer while smoking decreases. This indicates the Epidemiological findings are false. The inflexible medical approach that rules out any possibility of escape from the "risk" of smoking is absurd in the face of people like me who are NOT addicted, do not react to ETS and also from smokers who smoke all their lives and die of old age, and people who NEVER smoke, avoid contact and die of lung cancer.

The above write up or report, stem from my own experience. I have noted others come to the same conclusions independently also. I feel that the loss of testing for cause has lost out to easy computer based studies that syphon off all the tax money that should be used to find "cause"

I intend to sell my home in California, where nothing is good enough, to live with my new wife in Texas at the home above in Dennison, until something gets us!.

Response:

The comment indicates confusion as to the probabilistic nature of risk. There are a number of active smokers who live well into old age too. The report does not contend that everyone in contact with ETS dies from ETS. Rather, a thorough examination of the epidemiological and toxicological literature leads the majority of scientists to conclude that ETS exposure is associated with a number of adverse health outcomes. The comment does not supply alternative scientifically valid studies to contradict those conclusions in the report linking specific adverse health outcomes to ETS.

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, pp. 643-676) 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 cotinine in babies who had died of 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 Mitchell et al. (1993) and Mitchell et al. (1997) 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 SIDS 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 (Thun, 2003), 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) (as cited in Cal EPA, 1997) 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 (National Center for Health Statistics, 2002, as cited in Milne, 2003). 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.

References in comment:

Crawford FG, Mayer J, Santella RM, Cooper TB, Ottman R, Tsai WY, Simon-Cereijido G, Wang M, Tang D, Perera FP (1994). Biomarkers of environmental tobacco smoke in preschool children and their mothers. J Natl Cancer Inst. 1994 Sep 21;86(18):1398-402.

Reynolds P, Hurley S, Goldberg D. (2004) RE: Active Smoking, Household Passive Smoking,and Breast Cancer: Evidence From the California Teacher's Study. Response. J Natl Cancer Inst. 2004 July 7:96(13):1041-1043.

Wong, L. S.; Green, H. M.; Feugate, J. E.; Yadav, M.; Nothnagel, E. A., and Martins-Green, M. Effects of "second-hand" smoke on structure and function of fibroblasts, cells that are critical for tissue repair and remodeling. BMC Cell Biol. 2004; 5(1):13.

References in Responses:

Blot WJ, McLaughlin JK (1998). Passive Smoking and Lung Cancer Risk: What is the Story Now? J Natl. Cancer Inst. Oct 7:90(19): 1416-17.

Bero LA, Glantz SA, Rennie D. (1994) Publication bias and public health policy on environmental tobacco smoke. JAMA Jul 13; 272(2) :133-136.

Celermajer DS, Adams MR, Clarkson P, Robinson J, McCredie R, Donald A, et al. (1996). Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. N Engl J Med 334(3):150-4.

Conway K, Edmiston SN, Cui L, Drouin SS, Pang J, He M, Tse CK, Geradts J, Dressler L, Liu ET, Millikan R, Newman B. (2002) Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. Cancer Res. Apr 1;62(7):1987-95.

Copas JB, Shi JQ (2000). Reanalysis of epidemiological evidence on lung cancer and passive smoking. BMJ 320(7232):417-8.

Glantz SA, Parmley WW (1995). Passive smoking and heart disease. Mechanisms and risk. JAMA 273(13):1047-53.

Hackshaw A, Law M, Wald N (2000). Lung cancer and passive smoking: Increased risk not disputed. BMJ 321(7270):1221-2

Helsing KJ, Sandler DP, Comstock GW, Chee E (1988). Heart disease mortality in nonsmokers living with smokers. Am J Epidemiol. 127(5):915-22. As cited in Cal EPA (1997); Health effects of exposure to environmental tobacco smoke. Final Report, September, 1997. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Sacramento, CA.

Johnson KC (2001). .Re: Passive smoking exposure and female breast cancer mortality. J Natl Cancer Inst. 93(9):719-20.

Law MR, Wald NJ (2003). Environmental tobacco smoke and ischemic heart disease. Prog Cardiovasc Dis 46(1):31-8.

Lightwood JM, Glantz SA (1997). Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. Circulation 96(4):1089-96.

Milne E (2003). Passive smoking: doubts about effectiveness of age adjustment. BMJ 327(7413):502.

Reynolds P, Hurley S, Goldberg DE (2004). Re: Active smoking, household passive smoking, and breast cancer: Evidence from the California Teachers Study – Response J Natl Cancer Inst. 96 (13) 1042-43. (Chapter 7)

Schmid P, Karanikas G, Kritz H, Pirich C, Stamatopoulos Y, Peskar BA, et al. (1996). Passive smoking and platelet thromboxane. Thromb Res 81(4):451-60.

Stamatakis KA, Brownson RC, Luke DA (2002). Risk factors for exposure to environmental tobacco smoke among ethnically diverse women in the United States. J Womens Health Gend Based Med 11(1):45-51.

Tang D, Warburton D, Tannenbaum SR, Skipper P, Santella RM, Cereijido GS, Crawford FG, Perera FP (1999). Molecular and genetic damage from environmental tobacco smoke in young children. Cancer Epidemiol Biomarkers Prev. 8(5):427-31.

Thun M. (2003). More misleading science from the tobacco industry. Delaying clean air laws through disinformation. BMJ 3:352-353. letter.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, et al. (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ, doi:10.1136/bmj.38146.427188.55 (pub 30 June 2004).

Comments of J. Daniel Heck, Ph.D., DABT, Patricia Martin, Ph.D., DABT and Carr J. Smith, Ph.D., DABT, Scientific Affairs, for the Lorillard Tobacco Company

Preface

Comment on 6.2.1.2. Asthma induction in adults

The Cal/EPA 2003 draft report's conclusion that ETS exposure is causally associated with "adult-onset" asthma is at odds with the judgements of a number of authoritative scientific bodies that have recently reviewed available epidemiological data on this topic. Cal/EPA should seriously and objectively reconsider its conclusion in regard to "adult-onset" asthma causation to conform to contemporary standards for such scientific judgements.

Comment 1:

Cal/EPA's judgment is at odds with that of authoritative scientific bodies

The National Academies of Science' Institute of Medicine has very recently performed a thorough and exhaustive assessment of available evidence in regard to environmental factors that may cause or exacerbate asthma in adults and children (IOM – Clearing the Air 2000). The IOM report concluded that, among the many exposures considered, only house dust mite antigen had been demonstrated with sufficient evidence to cause the development of asthma. The IOM's consensus opinion in regard to ETS as a causative factor in the development of asthma in school-aged children, older children and adults was that there is *"...inadequate or insufficient evidence to determine whether or not an association exists..."* Similarly, IARC researchers had stated earlier (Tredaniel *et al*., 1994) that it "*..remains controversial..."* whether indoor air ETS is associated with chronic respiratory symptoms and asthma. Neither did the 1986 report of the US Surgeon General, the 1986 NRC report, nor the 1992 EPA report on ETS conclude that the evidence for ETS was sufficient to support a causal inference for "adult-onset" asthma.

Response:

There are number of reasons why the conclusions of the Cal/EPA differ from other evaluations, such as that published by IARC researchers in 1994 and the IOM in 2000. In the case of the association with asthma, we include some studies and meta-analyses that were unavailable to the IARC researchers and IOM at the time of their reports. This includes an update of the OEHHA staff's meta-analysis of ETS and childhood new onset asthma. OEHHA staff and consultants also undertook different (and in some cases more extensive) analyses of than those used by IARC and others. .

Comment 2:

The remarkable Cal/EPA draft assertion that "adult-onset" asthma has been shown conclusively to be causally associated with ETS exposures falls far short of the standards for such scientific judgments and should be withdrawn in a draft revision.

The etiology of asthma is only *incompletely understood*, and is *far too complex* to justify a simplistic inference of causation from a limited number of inconsistent epidemiological studies having inadequate confounder adjustments and at best weakly positive statistical associations with indoor air ETS exposures.

A bewildering genetic heterogeneity underlies the development of asthma; the scientific literature contains hundreds of genetic association studies on asthma-related phenotypes, with variants in 64 genes reported to be associated with asthma or related traits in at least one study (*1*). None of the nine new studies cited in the Cal/EPA 2003 draft included consideration of this variable in the diverse study populations.

While the new epidemiological reports cited by Cal/EPA in support of a causal inference for "adult-onset" asthma in association with ETS exposure included some adjustments for confounders, none of the individual studies has come close to adequately considering the full spectrum of diverse associations that have emerged as potentially potent confounders for this complex disease. One example of such an emerging confounder is described in a very recent systematic review of extant literature that found that aspirin-induced asthma is detectable in fully 21% (14-29%, 95% C.I.) of adults when definitive oral provocation testing is conducted (*2*). Notably, only about 3% (2-4%, 95% C.I.) of adults in this analysis were aware of such aspirin sensitivity and reported it at interview. This recent observation documents the imprecision and limited utility of self-reported symptoms in diseases of extraordinarily complex etiology such as asthma, and indicates that simplistic inferences of causation based upon such data are unlikely to be correct. Among the new "adult-onset" asthma reports cited by Cal/EPA (2003), 7 of 9 studies employed unreliable self-reported asthmatic symptoms or self-reports of asthma diagnosis.

Notably, the two cited studies that included more objective physician-diagnosed asthma data (Kronqvist, 1999; Flodin, 1995) did <u>not</u> report statistically significant associations of asthma and ETS exposure.

Cal/EPA should objectively consider the available data on the unreliability of such self-reported asthma symptoms in drawing conclusions of causation that are at odds with those made in previous and more rigorous assessments by other scientific and public health bodies.

Response:

Self-reported physician diagnosed asthma is a standard epidemiologic tool used to identify persons with asthma (Toren et al., Dodge and Burrows, 1980; Dodge et al., 1986; 1993; Burrows et al., 1991). It has been shown to be reliable and valid (Toren et

al., 1993; de Marco et al., 2004). Definitions of asthma based on asthma symptoms and / or asthma medication use are also widely accepted epidemiologic tools that have notably been used in the highly regarded European Community Respiratory Health Survey (Basagana et al., 2004; ECRHS 1995; Bjornsson et al., 1994; Jarvis et al., 1994; Burney et al., 1989; Burney et al., 1994).

Taken together, the studies have controlled for a broad array of potential confounding variables. One cannot exclude the possibility of residual confounding, of course, but it seems unlikely to explain these results. It is not valid to extrapolate the data from self-report of aspirin sensitivity to draw conclusions about self-report of asthma. Self-reported ETS exposure is likely to be more accurate than self-reported aspirin sensitivity, as ETS exposure is an obvious environmental entity whereas aspirin sensitivity is an immunologic phenomenon that may not be obvious to the subject. To argue that aspirin sensitivity is a confounder in the ETS-asthma relationship one would have to assume some association between aspirin sensitivity and asthma as well as an association between aspirin sensitivity and ETS exposure. There is no evidence nor reason to assume this that OEHHA is aware of and the commentator offers none.

Flodin did show increased risk, although the 95% CI included no effect which may be due to small sample size and lower statistical power; Kronqvist was a negative study as we acknowledged, but this was confined to a very select group, i.e., Swedish farmers. There is evidence that exposure during childhood to farming is protective (von Mutius 2002). Therefore, such exposure could obscure any adverse affects from ETS exposure; Jaakkola 2003 used a physician diagnosis and found a link between ETS and incident adult-onset asthma.

Comment 3:

Clinical studies of asthmatics exposed to experimental ETS have strongly suggested that reactions to ETS do not occur by the IgE-mediated mechanism that is a hallmark of classic allergic asthma (*16*). A minor subset of study subjects reporting ETS sensitivity and having clinically diagnosed asthma have been shown to react to experimental levels of ETS exposure with modest reductions in FEV_1. However, the detected responses appeared to be attributable largely to sensory irritation by constituents of the ETS gaseous phase and exhibited a clear exposure-response relationship for measurable effects in ranges far higher than those typically encountered (*16*).

Response:

These findings are restricted to acute responses that are more relevant to asthma exacerbation than to asthma induction. Longer-term effects from chronic lower levels of exposure such as airway remodeling and sensitization were not evaluated in the clinical study referred to in the comment.

Comment 4:

In the following text, the conclusions of Cal/EPA are addressed as summarized below:

1. Asthma is an exceedingly complex and incompletely understood disease; simplistic conclusions regarding its etiology, based upon weak statistical associations with environmental exposures, are at best tenuous.

2. The contention that ETS induces asthma in adults is supported by neither the weight and strength of available epidemiological evidence, nor by a compelling body of mechanistic evidence. No authoritative consensus judgement regarding causation of adult onset asthma by ETS has been made previously by any expert scientific/public health organization.

3. The entire body of available epidemiological data, including the nine new studies cited in the Cal/EPA 2003 document, is an entirely insufficient basis for a reasonable scientific conclusion of a causal association between ETS exposure and induction of adult asthma.

4. Major asthma risk factors include family history of atopic disease, atopy, exposure to house dust mites, cat dander, cockroach antigens and childhood obesity. The potentially confounding effects of these major asthma risk factors are difficult to control for in any epidemiological study.

5. ETS and respiratory health studies are difficult to conduct and interpret.

6. Real-world levels of ETS exposure, and particularly outdoor air levels, are trivially low.

7. The draft conclusion that ETS exposure causes "adult-onset" asthma is not consistent with contemporary scientific standards and should be withdrawn.

Response:

While we understand that good scientists and epidemiologists are appropriately reluctant to assign the term causative to an exposure without substantial and convincing evidence, we believe that indeed this hurdle has been cleared in the case of ETS and adult onset asthma. Some of the key factors are outlined below and our discussion has been expanded similarly in the revised document.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger et al. 1994), number of smokers in the environment (Leuenberger et al. 1994; Hu et al. 1997), duration of exposure to smoker (Leuenberger et al. 1994; Kunzli et al. 2000; Iribarren et al. 2001; Janson et al. 2001), duration of working with a smoker (Greer et al. 1993; McDonnell et

al. 1999), measured nicotine levels (Eisner et al. 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola et al. 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larsson et al., 2001), a defined period prior to the diagnosis of asthma (Flodin et al., 1995; Thorn et al., 2001; Hu et al., 1997; Greer et al., 1993; McDonnell et al., 1999), or a defined period prior to the development of asthma-like symptoms (Withers et al., 1998; Strachan et al., 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed a positive association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a causal association between ETS exposure and adult onset asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (California Environmental Protection Agency 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biological plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole et al., 1989; Comstock et al., 1981; Ng et al., 1993; Masi et al., 1988; O'Connor et al., 1987; Xu and Li, 1995; Schilling et al., 1977; Kauffmann et al., 1989; Brunekreef et al., 1985; Abbey et al., 1998; Carey et al., 1999; Jaakkola et al., 1995; Dimich-Ward et al., 1998; Eisner et al., 1998; Eisner 2002.

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of ETS exposure and incident adult asthma (Thorn et al., 2001; Hu et al., 1997; Greer et al., 1993; McDonnell et al., 1999; Jaakkola et al., 2003). Other studies have

prospectively examined the relation between ETS exposure and incident wheezing (Withers et al., 1998; Strachan et al., 1996). In addition, since the writing of the original draft of our document, a very useful paper has been published that provides the kind of gold standard evidence that has been difficult to obtain. This is a study in Finland by Jaakkola, et al (2003)AJPH, 2003;93:2055-2060), which was a large population based incident case-control design in a system that had the advantage of being able to define all incident cases of new onset asthma diagnosis. Diagnosis was based on clinical examination and included lung function measurement. Recruitment was aided by being able to identify via National Social Insurance records all patients who had received reimbursement for asthma medications and included 521 newly diagnosed case patients out of a population of over 440,000. The risk of new onset asthma in adults age 21-63 was doubled in those exposed to workplace ETS (OR 2.16, CI 1.26, 3.72) and nearly five fold in those with home exposure (OR 4.77, CI 1.29-17.7). Cumulative exposure over a lifetime at work and at home increased risk. This study indicates that cumulative lifetime exposure to ETS increases the risk of adult-onset asthma. A summary of this paper is included in the revised document.

The population-based study by Jaakkola and colleagues provides the strongest corroborating evidence to date that ETS exposure causes adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of incident adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

Comment 5:

Major Asthma Risk Factors

Boushey *et al*. (2000) provide the following descriptions of asthma risk factors:

> "The strongest is a family history of atopic disease."
>
> "Atopy greatly increases the risk of asthma."
>
> "This has best been established for the house dust mite…Other allergen exposures linked to a heightened risk of asthma are cat dander, cockroach, …"

Response:

Comment noted. OEHHA agrees that these are important risk factors for asthma.

Comment 6:

"In Britain and the United States, the rise in asthma among children has been accompanied by an almost epidemic increase in the prevalence of obesity."

Response:

This is an ecological association and therefore is not able to identify whether obesity predates, is coincidental to or is a consequence of asthma. Therefore, this study has no ability to assess the relationship between obesity and asthma at the individual level or to impart new insight on the ETS-adult asthma onset link.

Comment 7:

A very recent longitudinal study of "adult-onset" asthma among members of a New England HMO found that new-onset asthma cases were overwhelmingly more likely to have occurred in association with infection than in association with workplace/environmental exposures (Sama *et al*., 2003).

Response:

This does not in any way affect the interpretation of data focusing on ETS and adult asthma. Viral infection is associated with asthma. However, asthmatics are more likely to suffer respiratory infections so infections may or may not predate the onset of asthma. If the study didn't determine the temporal relationship, then adjusting for infections could obliterate associations from other causes by 'over controlling', which would explain the findings by Sama et al.

Comment 8:

Therefore, it is very important in any ETS-asthma epidemiological study to account and adjust, fully and accurately, for the major risk factors for asthma. The available studies to date that are cited by Cal/EPA do not fully meet this requirement.

Response:

There is no evidence, uncovered by the OEHHA review nor is any evidence presented here in the comment, that the ETS-asthma onset association is explained by unmodeled confounding. Importantly, the evidence that obesity is a cause of asthma is speculative only, so confounding by obesity is unlikely. Multiple confounders are considered and adjusted for in studies from around the world and the preponderance of evidence points to a role of exposure to tobacco smoke in asthma causation.

Comment 9:

Difficulties In Conducting And Interpreting ETS And Respiratory Health Studies

ETS and Respiratory Health in Adults

Respiratory diseases and symptoms in either healthy or compromised adults exposed to ETS have not been as widely studied as they have been in children. No clear picture emerges from an analysis of the published papers on this subject, because the literature reports positive and negative associations as well as non-associations.

The ETS studies on adult respiratory health are influenced by many of the same potential confounders as the childhood studies, but there are at least 5 factors that may be of increased importance in considering design of ETS studies in adult populations: 1) Presence of adult lifestyle confounders (*e.g*., alcohol consumption, dietary habits, hobbies such as woodworking and ceramics, *etc*.). 2) Occupational exposures to lung irritants. 3) Difficulty in obtaining accurate lifetime medical histories. 4) Greater difficulty in estimating current and past ETS exposure because of the increased mobility of adults. 5) Increased possibility of psychological aversion to ETS, resulting in exacerbation of reported symptoms (Smith *et al*., 1992).

In addition to the potential confounders noted above, a number of possible biases are important considerations in ETS studies. These biases include misclassification of smokers as nonsmokers, reporting bias including recall bias, and diagnostic bias.

Response:

All epidemiologic studies are subject to the classes of bias 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 included in this report were selected based on having met the standards of quality for conducting and reporting observational studies. Although no epidemiologic study can completely rule out bias, the consistency of results across many study designs conducted in multiple populations and locations around the world, it is unlikely that all studies suffer from a common systematic error. This consistency supports a causal association between the risk factor and the disease. Those studies that more adequately accounted for bias and confounding were considered of higher quality in this review and were weighted accordingly.

Comment 10:

Analysis Of Nine Asthma Studies Not Considered In 1997 Cal/ Epa Document

The Cal/EPA 2003 draft report states that the 1997 OEHHA report reviewed studies evaluating the relationship between ETS exposure and chronic pulmonary disease among adults, including asthma. They concluded "… ETS exposure may make a significant contribution to chronic respiratory symptoms in adults." Although the OEHHA reported in 1997 on five studies purportedly supporting an association between ETS exposure and "adult-onset" asthma (Dayal *et al*., 1994; Greer *et al*., 1993; Leuenberger *et al*., 1994; Ng *et al*., 1993; Robbins *et al*., 1993) no specific conclusions were articulated about asthma *per se*. Cal/EPA 2003 presents nine recent epidemiological studies that evaluated the impact of ETS exposure on new-onset adult asthma and, remarkably, draws an affirmative causation conclusion.

The nine studies listed in Cal/EPA 2003 Table 6.14 have been reviewed and a summary of their design features is listed in Tables 1 and 2 with written comments following. Table 1 lists author/reference, study type, variables tested, population studied, and country. In addition, Table 1 summarizes criteria used to establish smoking status (smoker vs non-smoker), lab confirmation of smoking status, ETS exposure assessment, and known (established) home and occupational exposures/confounders. Where possible, Table 2 summarizes author definition of asthma and assessment/diagnosis of asthma. Categorizations include self-reported asthma or symptoms of asthma; self-reported physician diagnosed asthma; physician diagnosed asthma; and medical (clinical testing) confirmation of asthma.

An analysis of Tables 1 and 2 (attached) shows the inadequacies of the nine additional epidemiological studies regarding the purported contribution toward a conclusion of a causal association between ETS and adult onset asthma. For example, all nine studies rely on questionnaires, with only one study fully incorporating examination-based physician diagnosed asthma, and none fully confirm smoking status by laboratory test. In addition, only three of the nine studies are prospective in design, with the remainder being either cross-sectional or case control. Therefore, the study designs generally do not facilitate control for recall bias and preclude determinations of causality.

Cross-sectional studies are, in any event, inappropriate for the development of inferences of causation and temporal relationships between purported exposures and effects.

Response:

The determination of causation in the OEHHA report is made from the entirety of the evidence and not based on a single study or study design. Perhaps the most influential study to date is Jaakkola (2003) that restricted cases to incident adult asthma and used medical examination to establish a physician diagnosis of asthma. A clear association between adult onset asthma and exposure to ETS is found in this high quality study. Case

control studies are not necessarily weaker designs than cohort studies, as they are all nested within a cohort (actually or theoretically). Adequacy of exposure assessment, generalizability of the study population, along with many other factors must be considered in determining study quality.

It is standard procedure to define smoking by self-report, and not by laboratory methods, in epidemiologic studies. For example, the centers for Disease Control and Prevention uses the National Health Interview Survey to estimate smoking prevalence in the United States based on self-reported smoking behavior (MMWR, 2004). Self-reported ETS exposure is the standard in the field of epidemiology for studying diseases with long induction periods such as asthma (Benowitz, 1999; Jaakkola and Jaakkola, 1997). Biomarkers, of which cotinine is the most common, have short half lives and have limited usefulness in study of the onset of diseases with long induction periods (Benowitz, 1999; Jaakkola and Jaakkola, 1997; Daisey, 1999). There are numerous studies that validate the use of self-reported ETS exposure (Coghlin et al., 1989; Coultas et al., 1989; Coultas et al., 1990; Cummings et al., 1990;Cunningham et al., 1996; Eisner et al., 2001; Emmons et al., 1996; O'Connor et al., 1995; Willemsen et al., 1997).

Comment 11:

Kronqvist et al., 1999

A large population-based cross-sectional study examined risk factors associated with asthma and rhinoconjunctivitis in 461 Swedish farmers. The farmers received a medical examination comprising a skin prick test (SPT), radioallergosorbent test (RAST) analyses, and lung function measurements. A questionnaire established symptoms and exposures. Subjects with a history of episodic shortness of breath, wheezing, and breathing difficulties were defined as having asthma. Allergen sensitization, especially to mites (OR=5.8 vs OR=3.8) and pollens (OR=10.3 vs OR=5.8) was significantly associated with asthma and rhinoconjunctivitis, respectively, in this farm community. Exposure to ETS in childhood and current exposure did not seem to affect the risk of allergen sensitization among either smokers or nonsmokers. No ETS data were given

Cal/EPA 2003

"By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. ETS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of ETS exposure, past or present, was associated with the risk of asthma (OR or RR were not reported) (Table 6.14)."

Heck et al. *Comments*

The study was relatively large and included 461 Swedish farmers receiving medical exam, SPT, RAST analyses and lung-function measurements. The authors noted the following: "Reported exposure to environmental tobacco smoke in childhood or currently

did not significantly affect the risk of airway disease in smokers, ex-smokers, or nonsmokers."

Response:

It is unclear what is meant by the comment that "no ETS data were given" as ETS exposure was assessed for the current period (home and work) and during childhood. This is a negative study, but was confined to Swedish farmers. There is evidence that exposure during childhood to farming is protective (von Mutius 2002). Therefore, such exposure could obscure any adverse effects from ETS exposure. As noted above, OEHHA relied on a number of studies, not just a single study, in concluding there is adequate evidence of a causal association between ETS exposure and adult onset asthma.

Comment 12:

Iribarren et al., 2001

This large cross-sectional study examined *current* exposure to ETS and the association with personal characteristics and self-reported health conditions as determined from a multiphasic health check-up between 1979 and 1985. A total of 47,472 adult never-smoking members of the Northern California Kaiser Permanente Health Plan undergoing multiphasic health check-ups between 1979 and 1985 participated in the study. A written questionnaire was used to record duration and location of ETS exposure. Although it is not clear exactly when the ETS exposure data were collected it appears at least partially retrospective.

The authors conclude ETS exposure correlates with several personal characteristics potentially associated with adverse health outcomes. They state ETS exposure was associated with several self-reported acute and chronic conditions but that the study design precluded causal inference.

Cal/EPA 2003

"Using a written questionnaire, current ETS exposure was ascertained for several locations: home, other small spaces (e.g., office or car), and large indoor spaces (e.g., restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any ETS exposure was associated with a greater risk of self-reported physician-diagnosed asthma or hayfever (OR 1.22, 95% CI 1.11-1.34 and OR 1.14; 95% CI 1.06-1.24, respectively), controlling for socioeconomic and demographic covariates. The risk estimates were similar for high level exposure ($\geq$ 40 hours/week) compared to no exposure. For weekly exposure duration, there was evidence of an exposure-response relationship among women but not men."

Heck et al. *Comments*

The authors noted the following limitations:

> "ETS exposure correlated with several personal characteristics potentially associated with adverse health outcomes."
>
> "Firstly, the design was cross-sectional, precluding temporal associations and inferences about cause and effect."
>
> "Thirdly, the assessment of medical conditions relied on self reports; no attempt was made to determine the sensitivity or specificity against a gold standard of care or serological markers."
>
> "Estimation of lifetime exposure to ETS ...was not possible in this cohort because duration of ETS exposure was not ascertained."
>
> "We found, unexpectedly, significantly lower odds of stroke among men reporting any ETS exposure at home or in large indoor areas."
>
> "Another noteworthy finding was the lack of association of self reported cancer or tumor with any source of ETS exposure individually or with total ETS exposure in either gender."

The manner in which the Cal/EPA draft presents its abbreviated review of the paper of Iribarren *et al*., (2001) is misleading in several respects, and should be revised to include and objectively discuss in their entirety the authors' peer-reviewed observations and conclusion that bear on whether ETS may be causally-associated with "adult-onset" asthma. These elements include the authors' admonition that cross-sectional studies such as that of Iribarren *et al*., (2001) cannot be legitimately employed to develop inferences of causation or temporal associations between environmental factors and the occurrence of "adult-onset" asthma.

The combination of "hay fever/asthma" for the purposes of this broad cross-sectional survey of health plan members unavoidably results in the combination of a variety of distinct disease conditions into a single symptom category. The selection of a few among the array of similarly weak and highly variable statistical associations among various lifestyle characteristics, behavioral traits, self-reported symptoms and ETS exposures reported in the original paper's Tables 4, 5 and 6 does not provide any reasonable basis for development of any conclusion of causation.

Response:

Causal inference cannot be based on a single study regardless of the study design. However, the consistency of results across several study designs, multiple populations and geographic locations supports causation. Iribarren et al. (2001) corroborates the findings from cohort and case-control studies. This is a cross-sectional study, so ETS exposure was assessed at the same time as the health conditions. This is clearly stated in the report.

Iribarren et al. are correct to be cautious about causal inference from a single cross-sectional study. However, it is a very large study that is highly generalizable to the general U.S. population. Taken together with the other studies, it provides supportive evidence that ETS exposure is associated with new-onset adult asthma. Including hay fever in the outcome definition could obscure the relationship between ETS exposure and asthma. This broader outcome definition is a limitation of the Iribarren et al. study.

Comment 13:

Larsson et al., 2001

A population-based study examined the impact of "at home childhood ETS exposure" on current self-reported physician-diagnosed asthma during adulthood. The participants included 8008 randomly selected adult never smokers (age 15-69) from Sweden. A questionnaire (postal survey) was used to estimate exposures, airway symptoms, and respiratory history. The authors concluded that, "childhood exposure to ETS is associated with an increased prevalence of asthma among adult never-smokers, especially in nonatopic subjects. Children exposed to ETS were also more likely to become smokers. ETS is a major lower airway irritant (LAWI)."

Cal/EPA 2003

"The prevalence of adult asthma was more common among subjects who indicated childhood ETS exposure (7.6%) compared to unexposed persons (5.8%) (p=0.035). Current self-reported "breathing difficulties from cigarette smoke" were also more common among subjects who indicated a history of childhood ETS exposure. In further analysis, the authors stratified by family history of asthma. Although there was no clear impact of ETS among subjects without a family history of asthma, ETS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28-2.58). These results could be consistent with higher rates of smoking cessation by asthmatic's parents, reducing exposure of their children with asthma."

Heck et al. *Comments*

Self-reported ETS exposure was assessed by the question, "Do or did any of your parents/relatives smoke at home when you grew up?" All questions were answered as either "yes," "no," or "not as far as I know." ETS exposures from smoking by parents or other relatives who actually live in the house is very different from that by relatives who occasionally drop by and smoke in the home. Also, there is no estimate of degree/intensity of exposure that may have occurred. It is unclear whether the self-reported current asthma began in childhood or is "adult-onset." Therefore, the relevance of these results to "adult-onset" asthma are also unclear.

The authors note "The difference in asthma prevalence between subjects exposed and not exposed to childhood ETS was more pronounced in the younger half of the population." The effect of recently-increased awareness of purported adverse effects of ETS on the

accuracy or consistency of the reporting by younger subjects was apparently not considered as a potential source of bias in the study.

"Wheezing" is not reported as significantly associated with ETS exposure. In fact, the *p* value for wheezing is 0.792, although wheezing is a hallmark symptom of asthma.

Additionally, the authors state "We cannot exclude the possibility of reporting bias where asthmatics are more prone than nonasthmatics to report ETS exposure, which would give an overestimation of the risk" and "...the association between active smoking and asthma is uncertain in the current literature."

Response:

Results from Table 5 of the article by Larsson et al. (2001) are consistent with those observed in the meta analysis of studies that examined ETS exposure and new-onset asthma in childhood. The risk was elevated and highly consistent among studies that controlled for allergic tendency and child's own smoking habits. Other results presented in the article are obscured by the lack of control for one or both variables.

The comment implies that the study age population was not relevant to the issues of "adult-onset" asthma. The majority of subjects were adults at the time of the study; all were older than 15 years. It is true that adult vs. childhood asthma onset cannot be completely distinguished, as the outcome was a lifetime history of physician diagnosed asthma. Childhood ETS exposure was also a risk factor for current wheezing and shortness of breath, supporting the contention that at least some of the ETS-related asthma onset occurred during adulthood.

The commentator was concerned about awareness on the part of some of the younger subjects of the health hazards associated with tobacco smoke influencing reporting by younger subjects. This is highly speculative as to potential to alter effect estimates related to childhood exposures. The new meta-analysis conducted by OEHHA staff and included in the revised document supports ETS exposure as causative in both young child and older child asthma. The data also is consistent with studies of older children finding a less pronounced impact on asthma compared to early childhood because the exposure measurement is less precise. This is the result of questions that ask more or less "is the child exposed to ETS" at the time of the study. In early childhood this is a closer estimate of lifetime exposure than in late childhood.

The comment also notes that wheezing, a hallmark symptom of asthma, was not reported as significantly associated with ETS exposure. This is true, but other hallmark symptoms of asthma, such as attacks of shortness of breath and breathing difficulties during exercise were associated with ETS.

Comment 14:

Janson et al., 2001

This cross-sectional study aimed to evaluate the effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey. The study included 7882 adult (age 20-48) never smokers from 36 centers in 16 countries. The authors report, "…passive smoking in the workplace was significantly associated with all types of respiratory symptoms and current asthma. No significant association was found between passive smoking and total serum IgE." The authors conclude that although, "passive smoking is common, the prevalence varies widely between different countries." The study reports, "passive smoking increased the likelihood of experiencing respiratory symptoms and was associated with increased bronchial responsiveness."

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"Compared with no ETS exposure, any ETS exposure at home or work was not associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84; 1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25; 2.88). There was no apparent impact of home exposure (OR 1.14; 95% CI 0.68; 1.90). These apparently discrepant results could be explained by the method of ETS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence with a smoker may not always reflect domestic ETS exposure (Eisner et al., 2001), use of this exposure measure could attenuate the effect estimate for home ETS exposure."
"The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea (nocturnal or exertional). In these instances, workplace ETS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. An exposure-response relationship was noted for all respiratory symptoms, but not clearly for asthma. Furthermore, both home and workplace ETS exposure were associated with greater bronchial hyper-responsiveness (assessed by methacholine challenge). Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between ETS exposure and self-reported asthma."

Heck et al. *Comments*

The study design was unblinded with "interview-led questionnaires." The percentage of cases classifiable as self-reported "adult-onset" asthma is unclear. Asthma was self-reported and subjects were not queried as to their age at onset and whether their reported asthma was physician-diagnosed. Thirty-six centers were studied, while only one used biomarkers of smoke exposure to validate nonsmoker status or ETS levels. The authors' abstract statement that "…passive smoking in the workplace as significantly associated with all types of respiratory symptoms and current asthma…" is inconsistent with the

95% confidence interval about the odds ratio and indicates a lack of statistical significance (odds ratio 1.90; 95% CI 0.90-2.88).

No significant association was seen between asthma and overall ETS exposure, asthma and household ETS exposure and ETS and total serum IgE. Reduction in lung function was not statistically significant in "ETS-exposed" participants.

In addition, the authors note a number of study limitations including cross-sectional design, possibility of recall bias and reliance on self-reported exposure. Cross-sectional studies are not appropriate as a basis for the development of inferences of causation.

Response:

The odds ratio for passive smoking and the risk of current asthma was 1.90 (95% CI 1.25 to 2.88) – see Table 2. This controlled for a large variety of potential confounding variables, including age, sex, parental smoking, sensitization to common aeroallergens, total IgE, and study center.

While there was no significant association seen between total serum IgE and ETS exposure, not all asthmatics have IgE elevation and not all persons with IgE elevation have asthma.

The statement about reduction in lung function not being statistically significant is inaccurate. Table 5 shows an exposure-response trend between daily passive smoke exposure duration and reduction of FEV1 (p=0.01 for trend; the highest exposure group had a statistically significant mean reduction of FEV1 of 63 ml compared to the unexposed group.

Of course, every study has limitations. The strengths of this study are its size, quality, and population based sampling (European Community Respiratory Health Study).

Comment 15:

Flodin et al., 1995

A population-based case-control study from semi-rural Sweden evaluated smoking as a possible determinant of "adult-onset" asthma (age $\geq$ 20 yrs), controlling for other factors such as air pollution at work, dwelling conditions, and atopy. The authors compared 79 cases of asthma, diagnosed between ages 20 and 65, with 304 randomly drawn population controls of similar age from the same area as the cases. A questionnaire was used to collect information on smoking habits, occupational exposures, dwelling conditions, various suspect allergenic exposures, and atopy. The authors note, "those who had smoked for 3 years or more, present or past, were at increased risk for bronchial asthma (adjusted odds ratio = 1.9; 95% confidence interval = 1.1-3.3)." Exposure to ETS at work involved a slightly greater but statistically insignificant risk (OR 1.5; 95% CI 0.8-2.5).

Cal/EPA 2003

"A population-based case-control study from semi-rural Sweden evaluated ETS exposure as a risk factor for adult onset asthma (≥age 20 years). During a 9 month period, cases were identified from all persons filling a prescription for beta-agonist medications in two communities. The diagnosis of asthma was confirmed by a pulmonary specialist. Controls were randomly selected from a general population register and matched to cases by age (of asthma diagnosis), gender, and community. ETS exposure at both home and work was assessed by written questionnaire, which was defined as exposure for at least 3 years prior to the age at asthma diagnosis (or comparable age for controls). Workplace ETS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8-2.5), but the confidence interval did not exclude no relationship. Exposure to ETS at home was not associated with a greater risk of asthma (OR 0.9; 95% CI 0.5-1.5)."

Heck et al. *Comments*

This study examines 79 persons with asthma who were 20-65 years at diagnosis. The study does not appear to separately examine smokers and nonsmokers. The risk for adult asthma in association with three years of self-reported ETS exposure at work was nonsignificant (adjusted OR = 1.5, 95% CI = 0.8-2.5).

At home the risk was actually less than 1.0 (OR = 0.9, 95% CI =0.5-1.9) for ETS-exposed subjects. Due to the reported lack of a statistically significant association and apparent failure to separately examine smokers and nonsmokers, this study does not support a causal association between ETS exposure and "adult-onset" asthma.

Response:

The study controlled for the potential confounding effect of smoking. Heck is alluding to effect-modification, which is a different issue. This is an overly simplistic argument – the risk was elevated and most of the 95% CI was on the side of increased risk. The small sample size resulted in decreased precision of the OR estimate, which is a limitation, but not a fatal one.

As regards the statement that the at home risk was actually less than one, this statement is misleading as the CI is quite wide and is also consistent with a near-doubling of the risk of asthma.

Comment 16:

Thorn et al., 2001

A Swedish population based case-control study examined self-reported exposures to mold and ETS in the home environment and the risk of "adult-onset" asthma. The study was performed in a random population sample (n=15,813), aged 20-50 years. The adult onset asthma cases for the study included subjects self reporting "physician-diagnosed"

asthma (n=174). Randomly selected referents (n=870) were chosen from the whole population sample. Exposures in the home environment, asthma, respiratory symptoms, smoking habits, and atopy were obtained from a comprehensive mailed questionnaire. Authors reported, "increased adjusted OR for asthma were associated with exposure to molds (OR 2.2, 95% CI 1.4-5.5) ETS (OR 2.4, 95% CI 1.4-4.1) and the presence of a wood stove (OR 1.7, 95% CI 1.2-2.5)."

Cal/EPA 2003

"A Swedish population based case-control study examined the impact of ETS exposure on "adult-onset" asthma (age $\geq$ 16 yrs). The investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, ETS exposure was associated with a greater risk of "adult-onset" asthma (OR 2.4; 95% CI 1.4-4.1). This increased risk was observed only among never smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2.0-11.6) than females (OR 1.5; 95% CI 0.8-3.1)."

Heck et al. *Comments*

The relative risks and confidence intervals for ETS (OR 2.4, 1.4-4.1) and mold (OR 2.2, 1.4-3.5) are so similar it raises the possibility that the two exposures are co-existent. The attribution of adult onset asthma to ETS may actually be confounded by mold which may or may not be evident to the subject.

When the relative risks for males and females are reported separately, the relative risk for females for ETS and adult asthma is non-significant, 1.5 (0.8-3.1).

The authors throw out data by starting with 251 cases of physician diagnosed asthma, then reducing the final subject number to 174 by arbitrarily reviewing only the period "between 1980 and 1994" purportedly to reduce recall bias. No report of the relative risks using the whole sample is given.

When all self-reported asthmatic symptoms are included in addition to self-reported physician diagnosed adult asthma, the risk becomes non-significant at 1.7 (1.0-2.8).

The authors note the possibility of both under- and over-reporting of ETS exposure in their study design.

Response:

The similarity of two odds ratios does not imply anything about the correlation between two predictor variables. In fact, examination of Table 2 shows that the prevalence of exposure to ETS and mold was quite different. For example, 47.8% of cases indicated exposure to ETS, whereas only 17.8% indicated mold exposure. There is no evidence that ETS exposure and mold are correlated.

The comment notes that relative risks for females alone is nonsignficiant. This is a statistical power issue, not a substantive issue.

The comment also notes that the authors "threw out data". The authors clearly describe their rationale for limiting the universe of cases to those who reported new-onset asthma during the period between 1980 and 1994, to enhance the likelihood of accurate reporting.

The comment notes that when all self-reported asthmatic symptoms are included in addition to self-reported physician diagnosed adult asthma, the risk becomes nonsignificant. The main outcome is incident adult-onset asthma, which was statistically significant.

Comment 17:

Hu et al., 1997

Asthma and related factors were evaluated in a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. Childhood ETS exposure to parental smoking was determined by parental reports. Seven years later during young adulthood, self-reported physician diagnosed asthma was determined using a written questionnaire. Family history was strongly associated with subjects' asthma (OR=3.1, 95% CI 2.4-4.5 for self reported physician- diagnosed asthma; OR=3.3, 95% CI 2.4-4.5 for current asthma). Exposure to parental smoking during childhood was significantly associated with self reported physician-diagnosed asthma (OR=2.9, 95% CI 1.6-5.6) and current asthma (OR=3.3, 95% CI 1.7-6.4). Also, self-reported mold growth at home was significantly associated with asthma (OR=2.0, 95% CI 1.2-3.2).

Cal/EPA 2003

"Hu et al. evaluated a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. At baseline, ETS exposure status was determined by parental reports of personal smoking. During young adulthood (seven years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental ETS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline (< one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in young adulthood (OR 1.8; 95% CI 1.1-3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1-2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma seven years later."

Heck et al. *Comments*

In this study, the age of onset for the reported asthma cases was not determined. Thus, the relevance of the findings to adult asthma onset is unclear.

Also, in this study, like others, there is a potential selection bias in selecting the cohort for study in that "…These subjects originally participated in a school-based smoking prevention study in 1986." The possibility of the unblinded subject correlating the current asthma "yes" or "no" question with the previous smoking cessation program cannot be excluded.

Response:

It is true that asthma onset would have occurred between the 7th grade, when most people are 12-13 years old, and the seven year follow-up, which would have occurred at 19-20 years old for most subjects. Consequently, asthma onset would have occurred during adolescence or early adulthood, which is best classified as "adult-onset" for most study subjects. In addition, there is no evidence that asthma that begins in adolescence vs. early adulthood is biologically different.

It is difficult to understand how participation in a school-based smoking prevention program could have introduced bias, selection bias or otherwise.

Comment 18:

Greer *et al*., 1993; McDonnell *et al*., 1999

A longitudinal cohort study of 3,914 adult non-smoking Seventh-Day Adventists living in California evaluated, by questionnaire, ETS exposure and the incidence of self-reported physician diagnosed asthma during a 15 year period. The authors reported the 10-year result (Greer et al., 1993) as relating asthma to occupational and ambient air pollution in nonsmokers. Similarly, the 15-year cohort follow-up (McDonnell et al., 1999) examined the incidence of asthma in nonsmokers with the long term ambient ozone concentrations. The Greer et al. (1993) study found: 1) ETS exposure significantly associated with the development of asthma (RR = 1.45; CI = 1.21 to 1.75), 2) airways obstructive disease before age 16 related to a marked increase risk (RR = 4.24, CI 4.03 to 4.45), and 3) an increased risk of asthma significantly associated with increased ambient concentration of ozone exposure in men (R = 3.12, CI = 1.61 to 5.85), but not in women.

The study by McDonnell et al. (1999) suggested that long-term exposure to ambient ozone is associated with development of asthma in adult males. The only ETS exposure associated with asthma was in nonsmoking females only, with weak relative risk, 1.21 (CI=1.04-1.39).

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"As reported in the 1997 Cal/EPA report, duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI= 1.2-1.8). Since the 1997 Cal/EPA report, longer-term follow-up of the cohort has been reported. At 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI= 1.04-1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma."

Heck et al. *Comments: Greer et al., 1993*

The representativeness of the Seventh Day Adventist (SDA) cohort to the broader California population is questionable. Furthermore, the prohibition of smoking by SDA church doctrine may increase the likelihood of smoker misclassification bias in this unique cohort. The ETS exposure is self-reported. The reported relative risk for adult asthma and ETS is very weak, RR 1.45 (CI =1.21-1.80).

The subject numbers of incident asthma cases are small, that is, N =51 for females and N = 27 for males.

Only 13% of the potential respondents did not answer the questionnaire, but the final cohort is 2/3 female. Whether more females were initially queried is unknown. The average age at time of enrollment is relatively high, that is, 56.5. The plausibility that after a lifetime of ETS exposure without developing asthma, asthma is then induced after the age of 56.5 is questionable.

Heck et al. *Comments: McDonnell et al., 1999*

ETS was associated with asthma in nonsmoking females only, with a weak relative risk, 1.21 (1.04-1.39). In addition, the authors note that, "Misclassification of asthma status may have been greater in females than males," and that, "The degree of obstruction represented by FEV_1/FVC was considerably larger in males than females (Table 2), and only 27% of the new female cases reported use of asthma medication compared to 61% of the males." Therefore, the reported statistically significant ETS/female association is not consistent with the study's clinical observations.

Response:

This group of Seventh Day Adventists is comprised largely of non-smokers, which makes them an ideal cohort to study the effects of indoor or outdoor air pollution. There is no available evidence that their religious practices reduce the generalizability of these results.

A 45% increase in risk in an assessment that was adjusted for important confounders has major implication for disease prevalence and population impacts for a common disease

such as asthma. Strong associations are neither necessary nor sufficient for causality and weakness is neither necessary nor sufficient for absence of causality (Rothman and Greenland 1998, pp. 24-28).

Comment 19:

Cal/EPA 2003 paragraph summarizing asthma induction discussion

"There is no "gold standard" for defining asthma in epidemiological research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma (McWhorter et al., 1989; Toren et al., 1993). Respondents' reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma (Toren et al., 1993). Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney et al., 1989)."

Heck et al. Comments

As shown in Table 1, there is significant heterogeneity in application of diagnostic criteria across the nine studies and in the general ETS asthma literature. While no diagnostic "gold standard" may be available, certainly minimum diagnostic standards should be used, as there is the possibility of a self-reported misdiagnosis especially with "adult-onset" asthma. Other conditions, for example the side effects of various drugs, could lead to a misdiagnosis. In general, actual physician diagnosis is superior to self-report.

Cal/EPA is correct in stating that there is no universally-accepted and entirely objective definition of asthma in epidemiology. Yet while Cal/EPA emphasizes the possibility that self-reported "asthma-like" symptoms may under-represent true asthma incidence, a more scientifically objective view would acknowledge that an imprecise definition of diseases would just as likely lead to over-reporting of common viral or bacterial respiratory infections as "asthma". Cal/EPA should revise its draft wording to fairly and objectively consider this reality.

Response:

While actual physician diagnosis may be a better measure of asthma than self-report of a physician's diagnosis as a measure of asthma, it is not feasible to do this in large-scale epidemiologic studies. Furthermore, as noted in earlier responses, many studies have demonstrated that self-reported physician diagnosis of asthma is a relatively robust way to ascertain asthmatic status.

Comment 20:

Conclusions

In summary, the nine new studies cited in the Cal/EPA 2003 document comprise: five foreign studies performed in populations and environments differing substantially from those of California; two studies of a Seventh Day Adventist cohort having numerous lifestyle differences from those of typical Californians;

Response

Indeed, the consistency of findings across samples drawn from populations around the world supports the ETS-asthma association.

Comment 21:

Four cross-sectional studies inappropriate for the development of inferences of causality; eight studies lacking a complete medical confirmation of asthma diagnosis; and a variety of additional deficiencies discussed above and itemized in accompanying Tables 1 and 2. A number of the studies represented by Cal/EPA as demonstrating an association between ETS and asthma development did not in fact report consistent statistically significant associations.

The Cal/EPA draft conclusion that ETS exposure is causally-related to the induction of "adult-onset" asthma cannot be justified by scientific standards. No other authoritative scientific bodies around the world have rendered a similar judgement upon examination of available epidemiological data. The simplistic conclusion that exposure to ETS is causally related to a complex, multifactoral, and incompletely understood disease condition such as "adult-onset" asthma is not supported by a compelling body of extant epidemiological data or supportive temporal and mechanistic data and should be withdrawn by Cal/EPA in its revision of the draft 2003 report.

Response:

Two prospective cohort studies (Hu and the Adventist Health Study,) support the association between ETS exposure and adult-onset asthma. The Adventist Health Study clearly studied incident, adult-onset asthma. Three population-based case control studies (Flodin, Thorn and Jaakola) and four cross-sectional studies reviewed in this document provide supporting evidence of an association between ETS exposure and adult-onset asthma. One case-cross over study (Eisner) and two cohort studies (Withers, Strachan) support an association between ETS exposure and adult-onset wheezing.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were

observed for total daily duration of ETS exposure (Leuenberger et al., 1994), number of smokers in the environment, (Leuenberger et al., 1994; Hu et al., 1997) duration of exposure to smokers (Leuenberger et al., 1994; Iribarren et al., 2001; Janson et al., 2001; Kunzli et al., 2000), duration of working with a smoker (Greer at el., 1993; McDonnell et al., 1999), measured nicotine levels (Eisner et al., 2001), and an ETS exposure index that incorporates both intensity and duration of exposure (Jaakkola et al., 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset and exacerbation.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larsson et al., 2001), a defined period prior to the diagnosis of asthma (Flodin et al., 1995; Thorn et al., 2001; Hu et al., 1997; Greer et al., 1993; McDonnell et al., 1999), or a defined period prior the development of asthma-like symptoms (Withers et al., 1998; Strachan et al., 1996). In these studies, exposure to ETS clearly predated the development of asthma.

In interpreting these epidemiologic studies, a critical issue is whether the observed association between ETS exposure and adult asthma could be explained by confounding factors. ETS exposure has been associated with younger age, female gender, non-white race, lower education, lower income, blue-collar occupation, and personal cigarette smoking (Iribarren et al., 2001; Hole et al., 1989; Mannino et al., 1997; Sippel et al., 1999). Many of these factors have also been associated with an increased prevalence of asthma and asthma-related morbidity (Mannino et al, 1998). All of the studies considered and controlled for potentially confounding variables. Overall, the observed relationship between ETS exposure and asthma appears to be robust and not explained by confounding.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a deleterious causal effect of ETS exposure on adult asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (Cal/EPA, 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function. (Hole et al., 1989; Comstock et al., 1981; Ng et al., 1993; Masi et al., 1988; O'Connor et al., 1987; Xu and

Li, 1995; Schilling et al., 1977; Kauffmann et al., 1989; Brunekreef et al., 1985; Abbey et al., 1998; Carey et al., 1999; Jaakkola et al., 1995; Dimich-Ward et al., 1998;Eisner et al., 1998; Eisner, 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association. In sum, examination of the Hill criteria supports a causal association between ETS exposure and adult-asthma onset.

References in Comments

Boushey, H.A., Corry, D.B., Fahy, J.V., 2000. Asthma, Chapter 39 in *Textbook of Respiratory Medicine*, Volume 2, Third Edition, J.A. Murray, J.A. Nadel (eds.), W.B. Saunders, Philadelphia, pp. 1247-1289.

California Environmental Protection Agency. 2003. Public Review Draft). Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, Part B: Health Effects. Chapter 6. Respiratory Health Effects, pp 1-104.

Dayal, H.H., Khuder, S., Sharrar, R., Trieff, N., 1994. Passive smoking in obstructive respiratory disease in an industrialized urban population. *Environ Res* 65(2):161-71.

Flodin, U., Jonsson, P., Ziegler, J., Axelson, O., 1995. An epidemiologic study of bronchial asthma and smoking. *Epidemiology* 6(5):503-5.

Greer, J.R., Abbey, D.E., Burchette, R.J., 1993. Asthma related to occupational and ambient air pollutants in nonsmokers. *J Occup Med* 35(9):909-15.

Hoffjan, S., Nicolae, D., Ober, C., 2003. Association studies for asthma and atopic diseases: a comprehensive review of the literature. *Respiratory Research* 4(1):14.

Hu, F.B., Persky, V., Flay, B.R., Zelli, A., Cooksey, J., Richardson, J., 1997. An epidemiological study of asthma prevalence and related factors among young adults. *J Asthma* 34(1):67-76.

IOM (Institute of Medicine), 2000. Clearing the Air: Asthma and Indoor Air Exposures. National Academy Press, Washington, DC.

Iribarren, C., Friedman, G.D., Klatsky, A.L., Eisner, M.D., 2001. Exposure to environmental tobacco smoke: association with personal characteristics and self-reported health conditions. *J Epidemiol Community Health* 55(10):721-8.

Janson, C., Chinn, S., Jarvis, D., Zock, J.P., Toren, K., Burney, P., 2001. Effect of passive smoking on respiratory symptoms, bronchial responsivemess, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. *Lancet* 358(9299):2103-9.

Jenkins, C., Costello, J., and Hodge,L., 1999. Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. *British Medical Journal* 328 (21 February):434-437.

Kronqvist, M., Johannsson, E., Perhage, G., Johannsson, S.G., van Hage-Hamsten, M., 1999. Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. *Allergy* 54(11):1142-9.

Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B, 2001. Enviromental tobacco moke exposure during childhood is associated with increased prevalence of asthma in adults. *Chest* 120(3):711-7.

Lehrer, S.B., Rando, R.J., and Lopez, M., 1999. The effects of environmental tobacco smoke on asthma: studies with a dynamic exposure chamber. In *Asthma: Causes and Mechanisms of an Epidemic Inflammatory Disease*, edited by T. Platts-Mills, Boca Raton, Florida: Lewis Publishers.

Leuenberger, P., Schwartz, J., Ackermann-Liebrich, U., Blasér, K., Bolobnini, G., Bongard, J.P., *et al*. 1994. Passive smoking exposure in adults and chronic respiratory symptoms (SALALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am J Respir Crit Care Med* 150(5 Pt 1):1222-8.

McDonnell, W.F., Abbey, D.E., Nihino, N., Lebowitz, M.D., 1999. Long-term ambient ozone concentraitonn and the incidence of asthma in nonsmoking adults: the AHSMOG study. *Environ Res* 80(2 Pt 1):110-21.

Ng T.P., Hui K.P., Tan W.C., 1993. Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. *J Epidemiol Community Health* 47(6):454-8.

Robbins A.S., Abbey D.E., Lebowitz M.D., 1993. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int J Epidemiol* 22(5):809-17.

Sama, Susan R., et al., Environ Health: A Global Access Science Source 2 :10 (2003).

Smith, C. J., Sears, S. B., Walker, J.C., and DeLuca P.O. 1992. Environmental tobacco smoke: Current assessment and future directions. *Toxicologic Pathology*. 20(2): 289-305.

Thorn J, Brisman J, Toren K (2001). "Adult-onset" asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy* 56(4:287-92.

Tredaniel, J., Boffetta, P., Saracci, R., Hirsch, A., 1994. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur Resp J* 7:173-.

Table 1. Summary of Exposure and Risk Factors: Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	Country	Study Type And Year conducted	Variables Tested	Population	Smoking Status Smoker vs Nonsmoker	Smoking status confirmed by lab test?	Exposure to ETS	Known Home exposures/ confounders considered	Known Occupational exposures/ con-founders considered
Kronqvist et al., 1999	Sweden	Cross-sectional 1996	Risk Factors	Population based 15-65 years dairy farmers (n=461)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire (especially for farmers)
Iribarren et al., 2001	Northern California USA	Cross-sectional 1979-1985	ETS esposure / personal characteristics	Lg health plan participants Never smokers 16,524 men (15-89) 26,197 women (15-105)	Questionnaire	No Subset only	Questionnaire (year collected not clear)	Questionnaire "lifestyle" factors	Questionnaire
Larsson et al., 2001	Orebro, Sweden	Population 1995-1996	ETS childhood exposure	Total of 8008 random inhabitants (15-69)	Questionnaire	No	Questionnaire	Some	Questionnaire
Janson et al., 2001	Europe	Cross-sectional 1990-1994	Passive smoking	7882 adults from 36 centres in 16 countries 3486 men; 4396 women (age 20-48) "never-smokers"	Questionnaire Self report	No	Questionnaire	Interview/ questionnaire "lifestyle" factors	Questionnaire Semi quant estimate from matrix of 350 occup. groups. Noted as none, low or high.
Flodin et al., 1995	Sweden	Case control 1990	Smoking	Population based 79 (20-65 yrs) w/ asthma 304 controls (age/sex)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Thorn et al., 2001	Alvsborg, Sweden	Retrospective case control, 1994	Mold or ETS	Population 15,813 (age 20-50)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Hu et al., 1997	LA and San Diego, CA, USA	Cohort 1993	Asthma related factors	n=2041 age 20-22	Questionnaire Self report	No	Questionnaire	yes	Not noted
Greer et al., 1993	SF, LA or San Diego, CA, USA	Long term prospective Cohort 1977; 1987	Occupational & ambient air pollution	n=3914; Adult (≥25 yrs) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Not noted	1987 included as part of questionnaire
Mc Donnell et al., 1999	SF, LA or San Diego CA, USA	Longitudinal prospective cohort; 1977; 1987; 1992	Long term ambient ozone concentration	n=3091 Adult (age 27-87) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Questionnaire	Questionnaire

Table 2. Criteria for Asthma Diagnosis : Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	Author Defined Asthma Symptoms	Questionnaire	Self reported Asthma or symptoms of asthma	Self Reported Physician Diagnosed	Physician Diagnosed Asthma	Medical Confirmation of Asthma symptoms
Kronqvist et al., 1999	History of episodic shortness of breath, wheezing, & breathing difficulties	yes	yes	no	yes	Allergic Disease Physician SPT (13 allergens) RAST (blood) Lung function test
Iribarren et al., 2001	Hay fever/ Asthma	yes	yes Hay fever/ Asthma	yes	no	Not noted
Larsson et al., 2001	Not noted	Yes – Developed from the British Medical Research Council questionnaire	Questions on many respiratory symptoms	yes	no	no
Janson et al., 2001	Not noted	Screening questionnaire Interview led questionnaire	Questions on many respiratory symptoms	no	no	Blood tests total and specific IgE, spirometry, methacholine challenge
Flodin et al., 1995	American Thoracic Society	American Thoracic Society	Beta-agonist users	no	Selected cases confirmed with doctor	Examined by lung specialist
Thorn et al., 2001	Not noted	1. Screening questionnaire 2. Mailed comprehensive questionnaire	Questions on many respiratory symptoms	yes	no	no
Hu et al., 1997	Not noted	questionnaire	yes	yes	no	no
Greer et al., 1993	Not noted	Questionnaire developed by British Medical Research Council	Questions on many respiratory symptoms	yes	no	1987 "cases" – 1990 medical record/physician confirmation
Mc Donnell et al., 1999	American Thoracic Society	American Thoracic Society	Questions on many respiratory symptoms	yes	no	Lung function testing Spirometry Peak expiratory flow (PEF)

References in Responses

Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL (1998).. Long-term particulate and other air pollutants and lung function in nonsmokers. American Journal of Respiratory and Critical Care Medicine 158:289-98.

Abramson M, Kutin J, Czarny D, Walters EH (1996). The prevalence of asthma and respiratory symptoms among young adults: is it increasing in Australia? J Asthma 33:189-96.

Basagana X, Sunyer J, Kogevinas M, Zock JP, Duran-Tauleria E, Jarvis D, Burney P, Anto JM (2004). Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. Am J Epidemiol 160:178-88.

Benowitz NL (1999). Biomarkers of environmental tobacco smoke exposure. Environmental Health Perspectives 107 Suppl 2:349-55.

Bjornsson E, Plaschke P, Norrman E, Janson C, Lundback B, Rosenhall A, Lindholm N, Rosenhall L, Berglund E, Boman G (1994). Symptoms related to asthma and chronic bronchitis in three areas of Sweden. Eur Respir J 7:2146-53.

Brunekreef B, Fischer P, Remijn B, van der Lende R, Schouten J, Quanjer P (1985). Indoor air pollution and its effect on pulmonary function of adult non-smoking women: III. Passive smoking and pulmonary function. International Journal of Epidemiology 14:227-30.

Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T (1989). Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. European Respiratory Journal 2:940-5.

Burney PG, Luczynska C, Chinn S, Jarvis D (1994). The European Community Respiratory Health Survey. Eur Respir J 7:954-60.

Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD (1991). Characteristics of asthma among elderly adults in a sample of the general population. Chest 100:935-42.

Cal/EPA (1997). Health effects of exposure to environmental tobacco smoke. California Environmental Protection Agency, Sacramento, CA.

Carey IM, Cook DG, Strachan DP (1999). The effects of environmental tobacco smoke exposure on lung function in a longitudinal study of British adults. Epidemiology 10:319-26.

Coghlin J, Hammond SK, Gann PH (1989). Development of epidemiologic tools for measuring environmental tobacco smoke exposure. American Journal of Epidemiology 130:696-704; as cited in . Cal/EPA (1997). Health effects of exposure to environmental tobacco smoke. California Environmental Protection Agency, Sacramento, CA.

Comstock GW, Meyer MB, Helsing KJ, Tockman MS(1981). Respiratory effects on household exposures to tobacco smoke and gas cooking. American Review of Respiratory Disease 124:143-8.

Coultas DB, Peake GT, Samet JM (1989). Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. American Journal of Epidemiology 130:338-47.

Coultas DB, Samet JM, McCarthy JF, Spengler JD (1990). A personal monitoring study to assess workplace exposure to environmental tobacco smoke. American Journal of Public Health 80:988-90.

Cummings KM, Markello SJ, Mahoney M, Bhargava AK, McElroy PD, Marshall JR (1990). Measurement of current exposure to environmental tobacco smoke. Archives of Environmental Health 45:74-9.

Cunningham J, O'Connor GT, Dockery DW, Speizer FE (1996). Environmental tobacco smoke, wheezing, and asthma in children in 24 communities. American Journal of Respiratory and Critical Care Medicine 153:218-24.

Daisey JM (1999). Tracers for assessing exposure to environmental tobacco smoke: what are they tracing? Environmental Health Perspectives 107 Suppl 2:319-27.

de Marco R, Pattaro C, Locatelli F, Svanes C (2004). Influence of early life exposures on incidence and remission of asthma throughout life. J Allergy Clin Immunol 113:845-52.

Dimich-Ward H, Lawason J, Chan-Yeung M (1998). Work shift changes in lung function in bar workers exposed to environmental tobacco smoke. American Journal of Respiratory and Critical Care Medicine 157:A505.

Dodge RR, Burrows B (1980). The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. American Review of Respiratory Disease 122:567-75.

Dodge R, Cline MG, Burrows B (1986). Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. American Review of Respiratory Disease 133:981-6.

ECRHS (1995). Prevalence of asthma and asthma symptoms in a general population sample from northern Italy. European Community Respiratory Health Survey--Italy. Allergy 50:755-9.

Eisner MD, Smith AK, Blanc PD(1998). Bartenders' respiratory health after establishment of smoke-free bars and taverns [see comments]. Jama 280:1909-14.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD (2001). Measurement of environmental tobacco smoke exposure among adults with asthma. Environmental Health Perspectives 109:809-14.

Eisner MD (2002). Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: impact on the general population and adults with current asthma. Environ Health Perspect 110:765-70.

Emmons KM, Marcus BH, Abrams DB, Marshall R, Novotny TE, Kane ME, Etzel RA (1996). Use of a 24-hour recall diary to assess exposure to environmental tobacco smoke. Archives of Environmental Health 51:146-9.

Greer JR, Abbey DE, Burchette RJ (1993). Asthma related to occupational and ambient air pollutants in nonsmokers. Journal of Occupational Medicine 35:909-15.

Hoffjan S, Nicolae D, Ober C (2003). Association studies for asthma and atopic diseases: a comprehensive review of the literature. Respiratory Research 4:14.

Hole DJ, Gillis CR, Chopra C, Hawthorne VM (1989). Passive smoking and cardiorespiratory health in a general population in the west of Scotland [see comments]. Bmj (Clinical Research Ed.) 299:423-7.

Hu FB, Persky V, Flay BR, Richardson J (1997). An epidemiological study of asthma prevalence and related factors among young adults. Journal of Asthma 34:67-76.

Iribarren C, Friedman GD, Klatsky AL, Eisner MD (2001). Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 55:721-8..

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P (1995). Passive smoking and evolution of lung function in young adults. An 8-year longitudinal study. Journal of Clinical Epidemiology 48:317-27.

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P (1996). Effect of passive smoking on the development of respiratory symptoms in young adults: an 8-year longitudinal study. Journal of Clinical Epidemiology 49:581-6.

Jaakkola MS, Jaakkola JJ (1997). Assessment of exposure to environmental tobacco smoke. European Respiratory Journal 10:2384-97.

Jaakkola MS, Piipari R, Jaakkola N, Jaakkola JJ (2003). Environmental tobacco smoke and adult-onset asthma: a population-based incident case-control study. Am J Public Health. 93(12):2055-60.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358:2103-9.

Jarvis D, Lai E, Luczynska C, Chinn S, Burney P (1994). Prevalence of asthma and asthma-like symptoms in young adults living in three east Anglian towns. Br J Gen Pract 44:493-7.

Jenkins C, Costello J, Hodge L (2004). Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. British Medical Journal 328:434-437.

Kauffmann F, Dockery DW, Speizer FE, Ferris BG, Jr (1989). Respiratory symptoms and lung function in relation to passive smoking: a comparative study of American and French women. International Journal of Epidemiology 18:334-44.

Kunzli N, Schwartz J, Stutz EZ, Ackermann-Liebrich U, Leuenberger P (2000). Association of environmental tobacco smoke at work and forced expiratory lung function among never smoking asthmatics and non-asthmatics. The SAPALDIA-Team. Swiss Study on Air Pollution and Lung Disease in Adults. Sozial- und Praventivmedizin 45:208-17.

Lehrer SB, Rando RJ, Lopez M (1999). The effects of environmental tobacco smoke on asthma: studies with a dynamic exposure chamber. In: Asthma: Causes and Mechanisms of an Epidemic Inflammatory Disease (Platts-Mills T, ed). Boca Raton, FL: Lewis Publishers, pp. 155-195.

Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, Brutsche M, et al. (1994). Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team [see comments]. American Journal of Respiratory and Critical Care Medicine 150:1222-8.

Mannino DM, Siegel M, Rose D, Nkuchia J, Etzel R (1997). Environmental tobacco smoke exposure in the home and worksite and health effects in adults: results from the 1991 National Health Interview Survey. Tobacco Control 6:296-305.

Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E, Kang DS (1998). Surveillance for asthma--United States, 1960-1995. Morbidity and Mortality Weekly Report. Cdc Surveillance Summaries 47:1-27.

Masi MA, Hanley JA, Ernst P, Becklake MR (1988). Environmental exposure to tobacco smoke and lung function in young adults. American Review of Respiratory Disease 138:296-9.

McDonnell WF, Abbey DE, Nishino N, Lebowitz MD (1999). Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. Environmental Research 80:110-21.

MMWR (2004). Cigarette smoking among adults--United States, 2002. Morb Mortal Wkly Rep 53:427-31.

Neukirch F, Pin I, Knani J, Henry C, Pison C, Liard R, Romazzini S, Bousquet J (1995). Prevalence of asthma and asthma-like symptoms in three French cities. Respir Med 89:685-92.

Ng TP, Hui KP, Tan WC (1993). Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. Journal of Epidemiology and Community Health 47:454-8.

O'Connor GT, Weiss ST, Tager IB, Speizer FE (1987). The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults [published erratum appears in Am Rev Respir Dis 1987 Aug;136(2):532]. American Review of Respiratory Disease 135:800-4.

O'Connor TZ, Holford TR, Leaderer BP, Hammond SK, Bracken MB (1995). Measurement of exposure to environmental tobacco smoke in pregnant women. American Journal of Epidemiology 142:1315-21.

Rothman, K. J. and Greenland, S. Causation and causal inference. Rothman, K. J. and Greenland, S. Modern Epidemiology. Pp. 24-28. Philadelphia, USA, Lippincott-Raven publishers.

Schilling RS, Letai AD, Hui SL, Beck GJ, Schoenberg JB, Bouhuys A (1977). Lung function, respiratory disease, and smoking in families. American Journal of Epidemiology 106:274-83.

Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML (1999). Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest 115:691-6.

Toren K, Brisman J, Jearvholm B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review [see comments]. Chest 104:600-8.

von Mutius, E (2002). Environmental factors influencing the development and progression of pediatric asthma. Journal of Allergy & Clinical Immunology 109(6 Supplement), S525-S532.

Willemsen MC, Brug J, Uges DR, Vos de Wael ML (1997). Validity and reliability of self-reported exposure to environmental tobacco smoke in work offices. Journal of Occupational and Environmental Medicine 39:1111-4.

Xu X, Li B (1995). Exposure-response relationship between passive smoking and adult pulmonary function. American Journal of Respiratory and Critical Care Medicine 151:41-6

Comments of Gina M. Solomon, M.D., M.P.H. (on behalf of the Natural Resources Defense Council), Barbara Brenner (on behalf of Breast Cancer Action), Jeanne Rizzo (on behalf of the Breast Cancer Fund), Bob Gould, M.D. (on behalf of San Francisco Bay Area Physicians for Social Responsibility) and Jonathan Parfrey (on behalf of Los Angeles Physicians for Social Responsibility)

Introductory Remarks

The Natural Resources Defense Council, The Breast Cancer Fund, San Francisco Bay Area Physicians for Social Responsibility, Los Angeles Physicians for Social Responsibility and Breast Cancer Action appreciate the opportunity to comment on the OEHHA draft health effects assessment for environmental tobacco smoke (ETS). Our organizations are all actively involved in efforts to prevent significant environmental threats to public health.

Comment 1:

The listing of ETS as a Toxic Air Contaminant (TAC) under Health and Safety Code sections 39650-39674 is a scientific "no brainer." There is a veritable mountain of scientific data showing that ETS is a significant health hazard, and is causally associated with cancer, cardiac disease, asthma, other respiratory disease, and developmental problems in children including Sudden Infant Death Syndrome (SIDS). It is absolutely clear that this chemical mixture qualifies for listing as a TAC. ETS contains numerous chemicals that are already listed as TACs, such as benzene, 1,3-butadiene, various polycyclic aromatic hydrocarbons (PAHs), acrylamide, ammonia, hexavalent chromium, formaldehyde, and lead. Another somewhat similar complex mixture, diesel exhaust, was listed as a TAC several years ago. Based on its list of ingredients, ETS could essentially be summarized as diesel exhaust with added nicotine and tobacco-specific nitrosamines (TSNAs). Therefore we strongly endorse the conclusions of the draft document and support the proposed listing of ETS as a TAC.

The draft health effects assessment is an agonizingly detailed review of the enormous scientific literature on ETS. Although the quality of the science is high, and we believe that the document accurately reflects the literature, we are deeply concerned that this review sets a standard that is ultimately detrimental to public health. Spending the decade of research and the thousands of person-hours required to create a document that is this lengthy and detailed for a TAC listing determination inevitably means that very few chemicals or mixtures will move through the listing process. As California implements increasingly severe budget cuts, it is likely that OEHHA will suffer from worsening staff shortages. If every document is expected to be a multi-volume review comparable to this draft, we will see very little activity toward listings of environmental hazards.

A prior document listing ETS as a toxic air contaminant was fully endorsed by the Scientific Review Panel in June of 1997. This document was begun in June of 2001 and was in process for two and a half years, during which time the California Air Resources Board did not have the authority to regulate ETS as a toxic air contaminant. Meanwhile, as we can see from this draft, we can reliably state that while this document was being written about three thousand children were born in California with low birthweight due to ETS exposures, three hundred infant deaths from SIDS occurred, hundreds of thousands of people suffered otherwise potentially preventable asthma exacerbations, and thousands of deaths from myocardial ischemia occurred due to exposures to ETS. Some number of these illnesses might have been prevented had ARB been granted the regulatory authority sooner to take aggressive action against ETS. It is therefore necessary for OEHHA to balance scientific thoroughness with its mandate to implement the laws designed to protect public health.

We firmly believe that it is possible to produce a high quality scientific review that is a fraction of the length of this document, and that could be completed in a small fraction of the time. There is nothing in the law or the science that requires OEHHA to produce a definitive encyclopedia on the effects of every chemical that it reviews. It is only the fear (and reality) of industry litigation, and the creeping precedent of ever-larger reports that drive OEHHA to such extremes in document preparation. Shorter review documents would save the time and effort of the agency scientists, and of the reviewers charged with reading the documents. Shorter documents can be just as accurate scientifically and can be much more useful for protecting public health, since five such documents could potentially be produced in the time spent on one document such as the one reviewed today.

Due to the extreme length of the document, we focused our review on the introductory material and the discussion of ETS and breast cancer. Although there are likely other important and interesting issues throughout the rest of the draft, we were simply unable to give these chapters the review they deserved in the time available.

Response:

OEHHA thanks the commentators for their remarks. While OEHHA is perhaps uniquely conscious of the volume of information and level of detail in the arguments presented in the document, we are unable to agree that a shorter document for this complex chemical mixture would address the legislative mandate that this process is designed to serve. Additionally, OEHHA was gratified to see that the similarly extensive document prepared in 1997 was seen as a useful contribution to the scientific debate on some of the (then) contentious issues relating to health effects of ETS exposure. It is hoped that the present update will similarly contribute to this ongoing debate, which requires careful and detailed consideration of the evidence, particularly where this extends or modifies the conclusions of the earlier document.

Comment 2:

Petition to Bring ETS before the DART Identification Committee

Although we did not focus our current review on Chapters 3-5 of the document, we could not help noticing that there is now even more extensive evidence demonstrating that ETS is a reproductive and developmental toxicant. In the interest of 'reducing, reusing, and recycling' this document, and in the hope of further protecting the public from this extremely hazardous exposure, we therefore petition OEHHA to take ETS out of the normal glacial prioritization process and to present these three chapters to the Developmental and Reproductive Toxicant Identification Committee at its next meeting for reconsideration of the listing of ETS under Proposition 65 [California Health and Safety Code 25249.5 et *seq]*

Response:

OEHHA have referred this request to the group responsible for Proposition 65 implementation. We are completing the process of public and peer review under AB 1807 before bringing the document to the DART Identification Committee in order to properly focus on the response to comments and revisions as appropriate to the document.

Comments on Chapter 1

Comment 3:

The definition of ETS is somewhat inconsistent with the discussion on page 1-4 and 1-5 about ETS exposure in animal studies. The latter discussion appears to state that only 'sidestream smoke' is relevant to ETS exposure, whereas the definition on page 1-2 makes clear that ETS is actually comprised of 'mainstream smoke' that escapes when the smoker inhales, exhaled mainstream smoke, and sidestream smoke. Thus the animal tests that carefully expose animals only to sidestream smoke do not appear to reflect the full range of realistic exposures to ETS. It is incorrect to say that "A few recent studies have used exposures characterized as 'sidestream smoke,' which is considered more relevant to the assessment of the effects of ETS exposure." In fact, a mixture of mainstream and sidestream smoke would be most relevant. Although this point is a minor one, it bears correcting to avoid the appearance of dismissing animal data that do not include only sidestream smoke. In reality, virtually all of the animal experiments could be classified as exposures to ETS at various doses.

Response:

OEHHA agrees in part with this comment. Our discussion on page 1-3 of what is sidestream smoke is correct. On page 1-6, the last sentence refers back to the previous sentence. We believe that sidestream smoke exposure in animal studies is important and more germaine to ETS than animal studies of only mainstream smoke, primarily because sidestream smoke is about 90% or more of ETS (U.S.EPA, 1992). The comment that a mixture of sidestream and mainstream smoke is the most relevant is correct. We have added a phrase to the last sentence and an additional sentence to clarify our meaning. The last two sentences of the paragraph now

read "A few recent studies have used exposures characterized as "sidestream smoke", which is considered more relevant to the assessment of the effects of ETS than studies of only mainstream smoke. Of course a mixture of exhaled mainstream and sidestream smoke would be most relevant."

Comment 4:

The discussion of measures of effect and weight of evidence evaluations on pages 1-5 through 1-7 is very useful. It does make sense to evaluate the quality of the studies and the sources and likely direction of any bias when evaluating the weight of evidence. It is also important not to dismiss studies that failed to achieve statistical significance at the 0.05 level, since such studies may indeed be affected by factors such as insufficient power or by extensive nondifferential misclassification of exposure. We also agree that inconsistencies in scientific results are almost inevitable in any body of research, and that the finding of results that are not consistent from one study to another should not be a reason to automatically dismiss the results or to give up and declare that 'the jury is still out' on an issue. Instead, it makes sense to try to determine if there may be explanations for the inconsistencies and to see if it is still possible to draw conclusions based on the entirety of the available evidence. It is helpful for OEHHA to explain these important issues in the introductory material to avoid confusion about how the draft was prepared, and to help members of the public understand these important scientific issues. We believe that this discussion reflects a thoughtful approach to the literature review that is well-justified scientifically.

Response:

Thanks for the comment. We hope that the reader understands we have considered the totality of the evidence, including information from carcinogenicity studies of ETS constituents (for example), and not just individual epidemiological studies .

Comments on Chapter 7 Section on Breast Cancer

Comment 5:

We applaud OEHHA for the groundbreaking review of the links between ETS and breast cancer on pages 7-91 to 7-155, and we agree with the conclusions reached. There has been a lot of important research over the past few years into this important issue, and the weight of evidence points strongly toward a causal association. The large majority of the epidemiologic studies found elevated odds ratios, although not all were statistically significant. The studies with the best efforts at exposure assessment found greater odds ratios and were more likely to achieve statistical significance, in keeping with the prediction that nondifferential misclassification of exposure status tends to bias toward the null. The literature on active smoking and breast cancer supports the unifying hypothesis that tobacco smoke is an important breast cancer initiator, but is also anti-estrogenic and therefore has an anti-promoter effect. Therefore the timing of the exposure becomes extremely important. Among smokers, exposure when the breast is still particularly vulnerable to carcinogens before pregnancy and lactation, appears to be clearly associated with breast cancer development, whereas exposure after pregnancy and lactation and

in the postmenopausal period has the opposite effect, especially in overweight women who would normally have higher levels of circulating endogenous estrogens after menopause.

Response:

OEHHA is appreciates these comments, which are in line with our overall conclusions on the association between ETS exposure and breast cancer.

Comment 6:

It is clear that tobacco smoke contains numerous chemicals that cause mammary tumors in laboratory animals. In addition to the fifteen chemicals listed in Table 7.4D, the following seven chemicals should also be added: acrylamide, isoprene, N-nitrosodiethylamine [1], propylene oxide, cadmium [2], nitromethane [3], and nitrobenzene [4].

Response:

OEHHA thanks the commentators for this additional information, and has modified Table 7.4D to reflect the occurrence and carcinogenic effects of these additional compounds. All the proposed additions were included, with the exception of cadmium, which, as noted in the footnote to the comment, is rather anomalous in that mammary tumors appeared in male rats only. (The critical study in fact included only male rats, but the result was not replicated in other somewhat similar studies in either sex.) Also the statistical significance of the result is fairly weak, and probably because of these features neither IARC in their most recent review (IARC Monographs, volume 58, 1993) nor NTP's 10th Annual Report on Carcinogens (ROC) chose to put emphasis on this result. All the other new entries have been validated by reference to the ROC or IARC. Additionally, the table was updated with new information on smoke composition, including values for the additional compounds, obtained from the newly published IARC monograph (Volume 83, 2004) on Tobacco Smoke and Involuntary Smoking. The revised table is shown below.

Table 7.4D Chemicals identified in tobacco smoke which induce mammary tumors.

Compound	Cigarette main-stream smoke (amount per cigarette) [i]	Cigarette side-stream smoke (amount per cigarette) [ii]	Cigarette smoke-polluted environments [iii]	Cigar (C) or Pipe (P) smoke (µg/100 g) [iv]	IARC Classification
Aromatic hydrocarbons					
Benzene	**28 - 106 µg**	**71 - 134 µg**	**5 - 22 µg/m^3**	**P: 34400 C: 9200-24600**	**1**
Benzo[a]pyrene	**5.6 - 41.5 ng**	**52 - 95 ng**	**0 - 3.6 ng/m^3**	**C: 1.8-5.1 P: 8.4**	**2A**
Dibenz[a,h]anthracen e	**4 ng**	[vi]			**2A**

[1] 9th Report on Carcinogens. US Department of Health and Human Services, Public Health Service, National Toxicology Program, 2000.

[2] IRIS http://www.epa.gov/iris/search.htm. Note that cadmium causes mammary tumors in male rats only.

[3] ToxNet (CCRIS-Chemical Carcinogenesis Research Information System): http://www.nlm.nih.gov/pubs/factsheets/ccris.html

[4] Gold LS, Neela B. Manley, Thomas H. Slone, Jerrold M. Ward. Compendium of Chemical Carcinogens by Target Organ: Results of Chronic Bioassays in Rats, Mice, Hamsters, Dogs, and Monkeys Toxicologic Pathology 29: 639-652 (2001).

Table 7.4D Chemicals identified in tobacco smoke which induce mammary tumors.

Compound	Cigarette main-stream smoke (amount per cigarette) [i]	Cigarette side-stream smoke (amount per cigarette) [ii]	Cigarette smoke-polluted environments [iii]	Cigar (C) or Pipe (P) smoke (µg/100 g) [iv]	IARC Classification
Dibenzo[a,e]pyrene	**Present**				**2B**
Dibenzo[a,h]pyrene	**Present**				**2B**
Dibenzo[a,i]pyrene	**1.7 - 3.2 ng**				**2B**
Dibenzo[a,l]pyrene	**Present**				**2B**
Nitrosamines					
N-nitrosodiethylamine	**0 - 25 ng**		**Up to 8.6 ng/m^3**		**2A**
N-Nitrosodi-*n*-butylamine	**0 - 3.0**				**2B**
Aliphatic compounds					
Acrylamide	**Present**				**2A**
Acrylonitrile	**8 - 39 µg**	**24 - 44 µg**			**2B**
1,3-Butadiene	**24 - 123 µg**	**81 - 135 µg**	**19 µg/m^3**		**2A**
Isoprene	**288 - 1193 µg**	**743 - 1163 µg**	**83 - 150 µg/m^3**	**C: 24500-63300**	**2B**
Nitromethane	**0.5 - 0.6 µg**				**2B**
Propylene oxide	**0 - 100 ng**				**2B**
Urethane	**20 - 38 ng**				**2B**
Vinyl chloride	**11 - 15 ng**			**C: 0.14-0.27**	**1**
Arylamines and nitroarenes					
4-Aminobiphenyl	**2 - 8 ng**	**21 – 32 ng**			**1**
Nitrobenzene	**25 µg**				**2B**
***ortho*-Toluidine**	**30 - 200 ng**				**2A**

Comment 7:

The findings of PAH-DNA adducts in humans exposed to environmental sources of polycyclic aromatic hydrocarbons, including cigarette smoke (ie. the Whyatt et al. study cited on page 7-136 and the Rundle et al. study described on page 7-91) are a helpful part of the causal chain. The fact that the PAH-DNA adducts do not appear to be a biomarker that is highly specific to cigarette smoke is not surprising, given the other environmental and dietary sources of this pollutant. Yet the finding of these adducts in human tissues, particularly in breast cancer tissues, does add to the overall weight of evidence, since we know that cigarette smoke is one important source of PAH exposure.

Response:

OEHHA agrees that the developing body of literature relating biomarkers of exposure to eventual outcomes is important and has continued to support the causal chain of evidence. Studies in humans now include evidence that levels of PAH-DNA adducts in normal breast tissue are related to tobacco smoke exposure and that levels of those adducts are associated with the likelihood of developing breast cancer. We have added several newer studies on these to the discussion in the revised document.

Comment 8:

There are a couple of inconsistencies between Table 7.4E on page 7-141 and the text that follows. In particular, the table classifies the Hirayama 1984 study and the Jee 1999 study as 'unlikely' to have missed important exposures to ETS. Yet in the subsequent tables these same studies are classified as 'likely' to have missed important ETS exposures. Because both studies looked only at the husband's smoking history, it seems at first glance that they should be classified as likely to have missed important exposures. However, since both studies were done in Korea during a time when perhaps it may have been unusual for women to work outside the home, occupational exposures may have been unlikely and such a history unnecessary. Still, it seems that the complete neglect of ETS exposures during childhood would merit classification of both studies in the 'likely' to have missed important exposures category, unless cigarette smoking was very unusual in Korea in the 1930's-1950's. At any rate, these studies should be classified consistently as either likely or unlikely to have missed important ETS exposures.

Response:

The text regarding these studies has been clarified. Hirayama and Jee are now listed in tables 7.4E and subsequently as likely to have missed important exposures. As you point out, the degree to which this may be true may be far less than studies from other regions due to cultural factors. In the summary statistics that follow table 7.4E they were already listed as likely to have missed important exposures and therefore no change in those numbers will be necessary.

Comment 9:

In this draft document, OEHHA calculates estimates of ETS-related morbidity and mortality due to a list of diseases, including California-specific figures for childhood asthma induction and exacerbation, bronchitis or pneumonia in children, lung cancer, SIDS, low birth weight, and otitis media. Yet for some reason, OEHHA fails to calculate estimates of ETS-related morbidity and mortality due to breast cancer. Such an omission makes no sense. OEHHA concludes correctly that the data support a causal association between ETS exposure and breast cancer. OEHHA is also able to calculate a summary statistic of the overall magnitude of the risk (a relative risk of 1.92 when all important ETS sources are collected). The overall population burden of breast cancer in California is well known. Therefore it would be straightforward to calculate the attributable fraction of breast cancer due to ETS. We searched the draft in vain for such a calculation and finally concluded that the calculation was omitted. It is critically important for the public to know the proportion of breast cancer occurrence in California that

would potentially be eliminated if exposure to ETS were prevented. Breast cancer is unfortunately all too common, and any public health intervention that may decrease the burden of this disease in California is of utmost importance. Therefore we strongly urge OEHHA to add a calculation of the attributable risk for breast cancer and ETS to the final version of this document.

Response:

We recognize the significance of our finding that ETS is a causative factor in breast cancer, and would like to see preventive measures taken as a result of our findings (not just for breast cancer but all the other endpoints associated with ETS). However, it is quite difficult to estimate attributable risk with any certainty given the number of known risk factors for breast cancer that contribute to the high rate of this disease including age at menarche, age at menopause, age at first birth, parity, and whether the woman breast fed her babies. Although perhaps a relatively crude attributable risk could be developed, we felt it was best to avoid the calculation until we have a better way to account for these other known risk factors.

Footnotes:

[i] IARC Monographs volume 83 (2004) Tobacco Smoke, citing preferentially Table 1.10 (the 1999 Massachusetts Benchmark Study), or else Table 1.14.

[ii] IARC Monographs volume 83 (2004) Involuntary Smoking, citing Table 1.3 (the 1999 Massachusetts Benchmark Study)

[iii] IARC Monographs volume 83 (2004) Involuntary Smoking, citing mainly Jenkins et al., 2000

[iv] IARC Monographs volume 38, Tobacco smoking and IARC Monographs volume 83 (2004) Tobacco Smoke.

[v] NTP: 10th Annual Report on Carcinogens (2002) unless otherwise indicated

[vi] Blank cell = no data available

[vii] IARC Monographs, Volume 3 (1973).

[viii] Cavalieri et al. (1989; 1991).

[ix] IARC Monographs, Volume 77 (2000).

[x] IARC Monographs, Volume 60 (1994).

[xi] IARC Monographs, Volume 65 (1996).

Comments of Mr. P. N. Lee M.A., C.Stat. (Consultant: P.N.Lee Statistics and Computing Ltd)

Part A Chapter 3

Comment 1.

While I am glad that my review on cotinine[1] has been cited (on page V-54), have no objection to being referred to as a consultant with tobacco industry involvement, and have no problems with the conclusions of my work as summarized in the Draft review, I found it odd that the paper is cited as "P.N.Lee, 1999" when all the other references in the Draft do not give initials. A similar citation is made on page V-61 and, amusingly, on page V-78, the reference to my paper appears between Pirkle and Poore and not in its correct alphabetical order.

Response:

Thank you for pointing out this irregularity. ARB and OEHHA staff are currently editing the document to correct these and other typographical anomalies that occur in the draft. ARB has corrected this citation to read Lee, 1999 and has put the reference in the correct order on page V-78.

Part B Chapter 3. Development Toxicity:

I: Perinatal Manifestations

3.2 Fetal growth

Comment 2.

The report considers that there is conclusive evidence of an effect of ETS on fetal growth. I disagree for reasons that are discussed in some detail in the enclosed review[2]. That review includes results from a large number of relevant epidemiological studies. The authors of the Draft chapter may find it useful to check whether, in Tables 1-3, I cite any papers they may have missed.

Response:

The 1997 document found conclusive evidence of an effect of ETS on fetal growth, and this conclusion received general support during the extensive processes of public comment and peer review to which that document was subjected. As discussed in the introduction to the present document, the purpose of this update was not to review or revisit conclusions drawn in the 1997 document, but to determine whether new evidence that has appeared since that time modifies the conclusion in any way. The conclusion of the present document is that new studies support and strengthen the conclusion reached in 1997 with regard to effects on birth weight.

In order to respond constructively to this comment we have extracted the key points from the review and respond to these individually. The Tables mentioned, and full citations of the sources, are available in the report submitted by Mr. Lee and available on line from his Web site. Citations in the responses refer to papers referenced in the OEHHA (2004) document unless otherwise noted.

Comment 3:

About 60 studies[1-61] have investigated the possible relationship of birthweight to ETS. Smoking by the father has been the most common index of ETS exposure, while other indices that have been used include smoking in the household, smoking at the workplace and the cotinine level of the mother.

Three main endpoints have been used for studying possible effects of ETS exposure on birthweight. One endpoint, used in many of the studies, is the difference in average birthweight between exposed and unexposed mothers. Another endpoint, used in some of the studies, is the risk of having a low birthweight (LBW) infant. This is traditionally defined as less than 2500g.[62] A third endpoint is the risk of having an infant that is "small for gestational age" (SGA).

In view of the known associations between maternal smoking and low birthweight[63] and between maternal and paternal smoking[1,64] most of the studies have restricted attention to nonsmoking mothers. However some studies have based their analyses on all mothers, in most cases making statistical adjustment for smoking.

Response:

Many studies reported separate analyses of non-smoking mothers (Dejmek et al., 2002; Windham et al., 2000; Jaakkola et al., 2001; Ahluwalia et al., 1997) and found elevated risk of low birth weight. Similarly, comparing the intensity of maternal smoke exposure via cotinine measurements with birth outcomes, Kharrazi et al. (2004) found a dose-dependent decrease in BW with increasing cotinine levels. We emphasize these studies in preference to studies that rely on statistical adjustment for maternal prenatal smoking.

Comment 4:

Numerous factors have been linked to low birthweight. These include the sex, parity and gestational age of the child, maternal age, the height and weight of the mother and father, socioeconomic and employment status, and maternal alcohol consumption.[65,66] The ETS/birthweight studies vary widely in the extent to which these factors have been taken into account. While 13 studies[22,27,29,31,40,43,47,48,54,58-61] have adjusted for eight or more factors, some of the studies do not correct for any factors at all. Despite evidence that nutritional factors play a role in birthweight[67] only two ETS/birthweight studies[30,34] have reported taking diet into account as a potential confounder.

Response:

For this reason, we give most weight to the studies that do make adjustments for confounding. We agree that controlling for maternal diet during pregnancy would help clarify the effects of smoke exposure. However, overall, the consistency of the findings argues for causality.

Comment 5:

Of 31 studies relating ETS to the risk of having an LBW infant, four[13,30,33,51] reported a significant ($p<0.05$) increase in risk, one reported a reduction that was marginally significant at this level[5], with the rest reporting no significant association.

Response:

Including studies described in the 1997 document, we present 22 estimates of the risk of LBW associated with ETS. This risk was elevated in the majority of cases with statistical significance attained in five studies, three of which were published since the first document. The absence of statistically significant findings in individual studies is not evidence of the absence of an effect. The association between ETS and LBW was found to be causal in the 1997 document after review by the Scientific Review Panel and the more recent studies support this assessment.

Comment 6:

Of 16 studies relating ETS to the risk of having an SGA infant, four[33,48,49,61] reported significant increases in at least one analysis, and one[40] a significant decrease.

Response:

As noted above, the absence of statistically significant findings in individual studies is not evidence of the absence of an effect. We conclude that the data taken as a whole are suggestive of an association between ETS exposure and small for gestational age.

Comment 7:

Most of the 42 studies looking for differences in birthweight associated with ETS exposure did not report a statistically significant relationship. However 12 studies[9,14,18,20,21,25,33,34,39,43,44,58] have reported a significantly reduced birthweight and one study[16] has reported a significant increase.

Interpretation of the reported associations is made difficult because:

- although increases in risk of LBW or SGA or reductions in birthweight associated with ETS have been reported in four[43,48,58,61] of the 13 studies that adjusted for eight or more potential confounding variables, these were only in isolated analyses for specific endpoints and exposure indices. Most analyses of these four studies showed no significant association.

Of the remaining nine such studies eight did not find any significant relationship at all, and one[40] reported a significantly lower risk of SGA associated with ETS exposure.

- some of the studies that have reported significant associations have accounted for no potential confounding variables[9,21,25,33,44,51] or have not restricted attention to nonsmoking mothers.[14,18,48]

Response:

In epidemiology, it is very common to have a number of studies that suggest a risk but do not in themselves reach statistical significance. In the body of evidence for ETS, there are a number of studies of the association between ETS and low birth weight that do reach statistical significance showing a decrement in body weight at birth. The findings of statistically significant elevation in risk of low birth weight associated with maternal ETS exposure, and elevated but not statistically significant risks in several other studies led to the conclusion of a causal association between ETS exposure and low birth weight in our 1997 report. This report was reviewed publicly and by peer review. In addition, studies such as Kharrazi et al (2004) that controlled for a wide range of potential confounders as well as maternal smoke exposure assessed by serum cotinine levels, found significant ETS effects on several birth outcomes including fetal death, SGA and LBW.

Comment 8:

Some of the ETS/birthweight studies[11,13,16,32,35,37,43,48,52] found that adjustment for potential confounding variables markedly weakened the strength of the reported relationship between ETS and reduced birthweight.

Response:

Since a number of factors may contribute to lower birth weights, it is expected that adjustment for them will reduce the apparent effects of ETS. The important point is that an association between birth weight and ETS remains after adjustment.

Comment 9:

Almost 30 studies have presented data on the relationship between birthweight and extent of ETS exposure. Only five of these[14,20,30,38,39] found a statistically significant trend. In two studies[20,38] the claimed effect is limited to the highest ETS exposure group, data by level of exposure not being shown in two of the other two studies.[14,39] Confounding, and other sources of bias, may contribute to an observed dose-response relationship.

Response:

These studies were published prior to 1997 and so were not reviewed for this update. While confounding may contribute to an association, studies that appropriately adjusted for confounding have found associations that are statistically significant between ETS exposure and

low birth weight. This finding was reviewed by the Scientific Review Panel on Toxic Air Contaminants in 1997. Our update strengthens this finding.

Comment 10:

Recent meta-analyses[68] estimate that ETS exposure is, on average, associated with a decrease in birthweight of 25 to 40g. This modest difference, of about an ounce, does not necessarily imply harm to the infant, and can be compared with a recent estimate of 102g for the reduction in birthweight relating to an elevation in altitude of 1000m.[69]

Response:

A recent study by Kharrazi et al (2004) examined birth outcomes in relation to maternal serum cotinine at 15-19 weeks of gestation. Over the range of cotinine values mean birth weight dropped 109 g. Of greater public health consequence was the observation that with higher maternal ETS exposures, a larger proportion of births were shifted to the lower tail of the birth weight distribution curve. There was no ETS exposure level below which birth weight was not reduced. Furthermore, low birth weight is a known risk factor for a number of adverse health outcomes including infant mortality. Thus a reduction in birth weight is considered a deleterious effect. A small reduction in birth weight for a baby that is already small can be serious.

Comment 11:

Reviewers have noted that in some studies the claimed effects of ETS on birthweight are far greater than would seem biologically plausible and are inconsistent with the results of the remaining studies.[70,71] One recent study, for example,[72] estimated, based on results for maternal smoking during pregnancy, that a 1000 ng increase in mean urinary cotinine was associated with a 59g reduction in birthweight, and that ETS exposure at home was associated with only a 21 ng increase in urinary cotinine. These results would suggest a birthweight reduction associated with ETS of about 1g, not the reduction of 50g or more reported in some studies,[9,12,17-21,28,34,43,44,46] many of which are small and take no, or only a few, potential confounding variables into account.

Response:

The more recent studies included in this update generally had better confounder control than the earlier studies cited above and consistently reported decrements in birth weight. The study by Wang et al (1997) mentioned above (as ref 72) reported a birth weight decrement of 57 g for women with urinary cotinine levels of 31-100 ng, which they say is a range found in passively exposed women. This value is similar to the range of birth weight decrements found in both this update and the previous document of 25-50 g. There is not necessarily a linear relationship between dose and birth weight decrement. Many studies have found substantially greater than 59 gm decrements with active smoking as has been well recognized. Overall, OEHHA feels that the data are consistent in finding an association between lowered birth weight and ETS exposure.

Comment 12:

Lack of objective measures of actual ETS exposure during gestation, and reliance on unverified paternal smoking as a measure of exposure, are additional flaws in the existing studies.

Response:

For this reason we give more weight to studies with objective measures of maternal exposure as, for example, the measure of maternal serum cotinine during pregnancy in the study by Kharrazi et al. (2004). It should be noted that exposure misclassification tends to bias towards the null; thus, evidence of an effect is even more striking.

Comment 13:

The evidence, taken as a whole, does not demonstrate that ETS exposure decreases birthweight or increases risk of LBW or SGA.

Response:

We do not agree with this interpretation. We do agree that the evidence for SGA is suggestive. The finding of an association between ETS exposure and LBW has already undergone our public comment and peer review process during the preparation of our 1997 report. The new studies support our previous conclusion.

Part B Chapter 4. Developmental Toxicity:

II. Postnatal Manifestations

Comment 14:

4.1 SIDS

The report considers that there is conclusive evidence of an effect of ETS on SIDS. I disagree for reasons that are discussed in some detail in the enclosed review[3].

Response:

OEHHA staff thanks Mr. Lee for his review, but disagree with his conclusion [and endorse their earlier conclusion (OEHHA 1997) finding an effect of ETS on SIDS], as noted in the following detailed responses.

Comment 15:

There have been a number of recent reviews of the association between SIDS and parental smoking[1,8,20,28]. When attempting to interpret the results relating to ETS exposure it is important to bear in mind the following points:

Some of the studies[10,11,13,25] reporting an association between SIDS and ETS exposure have not adjusted for any other risk factors, while many others[9,12,14,16,17,21,23,26,27] have only taken a few of them into account.

Response:

Consideration of other risk factors is a critical concern, especially in many of the older studies mentioned above. In general, the more recent studies included in this update had better control for confounding and continued to support a causal association.

Comment 16:

Four studies[15,18-20] have taken into account quite an extensive list of potential confounding variables in at least some of their analyses. In two studies[15,20], such adjustment explained about 80% of the increased risk of SIDS associated with maternal smoking after pregnancy, and in a third study[19] it explained about 50%. In the fourth study[18], adjusted results were not reported for maternal smoking after pregnancy, but adjustment markedly reduced the relative risk associated with maternal smoking in pregnancy, from 4.84 to 1.78. Since such adjustments will inevitably be incomplete - partly because not all such factors will have been considered, and partly because data errors or use of surrogate variables limit the ability to control for confounding - it is not implausible that all of the claimed SIDS/ETS association could in fact be explained by confounding.

Response:

Newborns are indeed vulnerable to a variety of environmental conditions that may contribute to SIDS, adjustment for which reduces the apparent risks associated with ETS. However the consistency of the association of SIDS with ETS exposure in a variety of studies after adjustment for multiple confounders reduces the plausibility that the SIDS/ETS association is wholly explainable by confounding. Furthermore, adjustment for all confounders is nearly impossible, and may actually result in over-controlling for confounders masking the ETS effect.

Comment 17:

In a recent study[29], infants with prolongation of the QT interval, as measured by electrocardiograph shortly after birth, had a more than 40-fold increased risk of SIDS. This abnormality, seen in 50% of the infants dying of SIDS, is a major risk factor that could not have been caused by postnatal ETS exposure and which has not been taken account of in any of the epidemiological studies of ETS and SIDS.

Response:

Recent experiments in rats may provide a link between an infant's smoke exposure in utero and prolonged QT interval. Alterations in cardiovascular responsiveness to neurotransmitters were seen in rats after prenatal exposure to nicotine at levels consistent with maternal smoking (Slotkin et al., 1999). This exposure was associated with an increase in cardiac muscarinic type

2 receptors (M2) on which acetylcholine acts to decrease contraction rate. Nicotine exposure has been shown previously to cause a decrease in ß-adrenergic receptors (Navarro et al., 1990) through which heart rate is stimulated. The combination of an increase in inhibitory receptors and a decrease in excitatory receptors would be expected to lead to dis-regulation of heart function, possibly manifesting as an increased QT interval. This study also reported a nicotine-induced reduction in brainstem muscarinic receptors paralleling that seen in infants who have died from SIDS. In these infants there was decreased binding in brainstem areas associated with cardiorespiratory functions (Kinney et al., 1995). Thus ETS exposure may contribute to the risk of SIDS by impairing the ability of the brain and heart to respond appropriately to periods of hypoxia especially in infants exposed to smoke components in utero.

Comment 18:

Even if the association between parental smoking and SIDS cannot fully be explained by uncontrolled confounding by other risk factors, it may result, not from ETS exposure but from an effect of maternal smoking in pregnancy. Some studies have found that the association of SIDS with postnatal maternal smoking or paternal smoking has been reduced[15,16,20] or even eliminated[21] if adjustment is made for maternal smoking in pregnancy or if attention is restricted to nonsmoking mothers, though others have not[14,19].

Response:

Infants whose mothers smoked during pregnancy are indeed at greater risk of dying from SIDS; however, postnatal ETS exposure is an independent risk factor that can exacerbate this effect. Thus a reduction in the apparent SIDS risk after adjustment for maternal prenatal smoking would be expected. Our estimate of SIDS risk for maternal postnatal smoking is from a meta-analysis of studies that controlled for maternal prenatal smoke exposure (Anderson and Cook, 1997). Yet higher risks (OR 3.50) and a dose response were found by Klonoff-Cohen et al (1995) for postnatal ETS from all sources after adjusting for maternal prenatal smoking and other risk factors.

Part B Chapter 6. Respiratory Health Effects

Comment 19:

6.2.1 Asthma induction

My colleagues and I are in the process of conducting an extensive review of the evidence on asthma induction and ETS. Currently, we have data from some 160 studies on our database and hope to analyse it in a month or two. When our conclusions are drawn, I should be able to make the report available.

Response:

OEHHA thanks the commentator for this advance notice and looks forward to seeing the report, although the proposed timetable makes it unlikely that any new materials identified or issues raised therein will appear in the next draft of the OEHHA document.

Part B Chapter 7. Carcinogenic Effects

Comment 20:

I have concentrated my comments on the data for adults, as I have not recently reviewed the data on childhood cancer. In any case, the conclusions reached in the Draft are not very different from those from my 1998 review on childhood cancer[4].

As regards cancer in adults, I have recently reviewed the evidence extensively. The relevant material for lung cancer is described below, while that for other cancers was reviewed in a published paper in 2002,[5] since updated in an unpublished review.[6] Copies of these are enclosed.

Below I present my comments on a site-by-site basis.

Response:

OEHHA thanks the commentator for the review papers supplied. OEHHA staff have read these and taken note of their content, although as explained elsewhere review papers are not automatically noted or abstracted in the OEHHA document.

Comment 21:

7.1 Total cancer risk in adults and ETS

A recent relevant study has been missed.[7]

Response:

OEHHA thanks the commentator for this suggestion. This study (Nishino et al., 2001) is referenced for several site-specific findings, elsewhere in the chapter, and described on page 46 of the draft. The result for all cancers will be added to the revised document.

Comment 22:

7.2 Lung Cancer and ETS

I find it extremely depressing that no mention whatsoever is made of the series of five papers that my colleagues John Fry, Barbara Forey and I published[8-12] in Indoor + Build Environment in reply to the review paper by Hackshaw *et al*[13] in the BMJ. These provide extremely detailed support for our view that the dose-response relationship between lung cancer and ETS exposure

may be plausibly explained by (i) bias due to smoking misclassification, (ii) confounding by fruit, vegetables, dietary fat and education, (iii) correction of errors in one published study, (iv) inclusion of results from all pertinent studies and (v) restricting attention to those studies that have adjusted for age. A set of reprints of the five papers is enclosed.

I also feel the report lacks meta-analyses. I enclose up-to-date meta-analyses[14] based on data summarized in another document,[15] also enclosed.

Response:

In spite of the difficulties in accessing the journal cited (it is not indexed in Index Medicus, and in fact covers a very wide range of topics principally of interest to the building industry: we are unsure of the extent of this journal's peer review process in regard to epidemiological statistics), staff is aware of Mr. Lee's extensive commentaries on the literature relating to environmental tobacco smoke, and have given his analyses due consideration. However, the papers in question were not selected for inclusion in the draft report because we had reviewed them in the public comment period during preparation of the 1997 report.

The draft report is not a de novo analysis of the entire literature on the subject, but rather an update of the OEHHA (1997) report, which treated the subject of lung cancer in particular in considerable depth. OEHHA has not revisited conclusions based on studies reviewed in the earlier document (which have the benefit of peer review both by the Scientific Review Panel for Toxic Air Contaminants and the general scientific community), except where OEHHA was convinced by new data and/or a revised analysis by our staff that a conclusion should be modified. In the case of the papers cited in the comment, the majority of the data included in the analysis predates the 1997 document and was considered therein. Also, many of the arguments are by no means new, and were addressed extensively in OEHHA's 1997 report, and in responses to comments received on the draft of that report. New studies have been included by reference to the primary publications in the scientific literature.

Comment 23:

7.3.1 "Nasal sinus cancer"

The report mistakenly considers cancers of the nasopharynx under this heading. The two cancers should be kept separate. The evidence for nasopharyngeal cancer is highly variable and most unconvincing, as described in my unpublished review of "the epidemiological evidence on environmental tobacco smoke and cancers other than the lung."[6] As is evident from that review, there is another relevant study that has been missed in the draft.[16]

The evidence on nasal sinus cancer is in fact no more than it has been for a number of years. Reasons why the evidence seems inconclusive are given in my review.[6]

Response:

The comment is correct and the text has been changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. It is of interest to note in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002) report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS would have similar effects in both sites.

As mentioned in our response to comment 47 by M. LeVois, 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 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, but 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 suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Comment 24:

7.3.2 Cervix cancer and ETS

Two relevant studies of ETS and cervix cancer have been missed.[7,17] For one of these[17] the title concerns lung cancer but relevant data on cervix cancer are included. See my review[6] for a summary of my views. We agree the data are inconclusive.

Response:

OEHHA thanks the commentator for these suggestions. These studies (Nishino et al., 2001; Jee et al., 1999) are described, and referenced for other site-specific findings, elsewhere in the chapter. The results for cervical cancers will be added to the revised document.

Comment 25:

7.3.3 Bladder cancer and ETS

There is a recent study on this not considered in the Draft.[18] The evidence remains not even suggestive of a relationship.[6]

Response:

OEHHA has added (Zeegers et al., 2002), which is primarily concerned with active smoking, to the revised draft document with regard to both active and passive smoking and bladder cancer.

Along with other investigators, these authors found clear evidence of an association between current or former active smoking and bladder cancer: adjusted incidence rate ratios were 3.3 (95% CI 2.4 – 4.6) and 2.1 (95% CI 1.5 – 3.0) for current and former smokers respectively, relative to lifetime nonsmokers. In contrast, exposure to parental smoking or high levels of ETS at work elevated bladder cancer risk, but not significantly (1.2, 95% CI 0.56; 2.4 and 1.4, 95% CI 0.70; 2.6, respectively). There was no evidence of an association between ETS exposure from an ex- or current smoking partner. It is questionable, however, how unexposed the reference population is since the estimate for work exposure compares "high" versus "low" ETS rather than ETS exposure with no exposure. The estimates based on partner smoking status (never, ex, current) do not reflect other potential sources of exposure to ETS. A more complete evaluation of actual ETS exposure is needed to adequately address the question of the role of ETS exposure in bladder cancer.

Comment 26:

7.4.1 Breast cancer and ETS

In view of the report of the Collaborative Group on Hormonal Factors in Breast Cancer[19] that concluded, based on reanalysis of data from 53 studies, that "smoking has little or no independent effect on the risk of developing breast cancer," it would seem extremely unlikely that ETS might cause breast cancer. For reasons discussed in my review,[6] the direct epidemiological evidence that it does so is extremely unconvincing. I regard it as quite amazing that the Draft should reach the conclusion that ETS definitely causes breast cancer.

Response:

As detailed below, and in the revised document, OEHHA disagrees with the assertion in this comment that there is no association between active smoking and breast cancer. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of spousal smoking habit as a sole, dichotomous measure of ETS exposure seems egregiously inadequate since it largely fails to capture the extent of exposure during the period of greatest sensitivity. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship, in this case this assumption is neither necessary, nor supported by the data.

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. The existence of a mammary carcinogenic effect of tobacco smoke is supported by numerous studies of its individual components, which include several IARC-recognized human carcinogens. Additionally, there are several explanatory hypotheses which can be advanced, with varying degrees of experimental and epidemiological support, for the non-linear dose response relationship. The existence of such plausible mechanistic hypotheses certainly provides support for OEHHA's analysis, but it is not necessary that any or all of these mechanistic hypotheses be proven beyond doubt; the key assumption of causality and non-linear dose response precedes the explanatory hypotheses rather than being derived from them. The pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer makes no claims of considering in any way passive smoke exposure. The analysis essentially divided smokers into never versus ever and ex versus current thus providing little information in the way of quantitative exposure to smoke. Under the methods section they state that "no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure". If, as we believe to be true, the data supports a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason) and if most non-smokers have had significant ETS exposure which is certainly the case, particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk. In effect, the analysis is to a large degree comparing exposed with exposed.

Reynolds et al. (2004) in their recent prospective study (which appeared subsequent to OEHHA's public review draft, but has now been added to the report), did find a significant association between active smoking and breast cancer that increased with increasing duration and intensity of smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66, 95% C.I. 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure.

Comment 27:

I believe that four relevant studies have been missed out.[20-23] Note that when all the relevant data are in, fixed effects meta-analysis shows no association, with a relative risk estimated as 1.06 (95% CI 0.99-1.14). See my review[6] for details.

Response:

Reference 20 (Hirose et al., 1996) is a study of cervical and endometrial cancer, not breast cancer, and is noted as such in the commentator's review paper. Is it perhaps possible that this citation is a cross-tabulation error and the paper Mr. Lee intended to reference is Hirose et al (1995), reference 35 in his review?

Hirose et al (1995) report a Japanese hospital-based case-control study (n = 560) of breast cancer classified according to menopausal status. A significant association between active smoking and breast cancer was suggested by several analyses, including a multivariate analysis considering the various confounding factors. They also found a significant risk for exposure to ETS, assessed as current spousal smoking status, in postmenopausal women, (OR 1.39, 95% CI 1.04; 1.85), but not for premenopausal women (OR 1.15, 95% CI 0.91; 1.46). Unfortunately, ETS exposure was not subjected to multivariate analysis to control for potential confounding. This study had the advantages of relatively large size and limited potential response bias due to the collection of data prior to disease diagnosis. However, being a hospital-based study limits the ability to generalize the results to the general population. The apparent link between ETS exposure and breast cancer as a function of menopausal status must be interpreted with caution since the analysis was not adjusted for potential confounders, nor did it take into account potential sources of ETS exposure other than spousal smoking. This paper is in the time frame where it would be expected to appear in the OEHHA (1997) review, but is not described there; perhaps there was a delay in access to the original publication. A note of this study will be added to the revised document in relation to active smoking, and referenced with regard to the ETS finding.

Reference 21: (Furberg et al., 2002) has been referred to by Mr. Lee and other commentators, to whom OEHHA is grateful for pointing out this omission. A description and commentary has been added to the document. The paper describes an analysis of data from a population-based case-control study of breast cancer (the Carolina Breast Cancer Study, also the subject of other authors' sub-analyses), which was designed to identify any difference in risk of p53 protein positive vs. negative breast cancer associated with a range of environmental exposures. No such difference was observed for any category of active or passive smoking examined. However, an association was observed for p53-negative breast cancer and long-duration (>20 years) smoking (OR relative to never smokers 1.5, CI 1.1 – 2.1). Small but non-significant elevations in OR for both P53+ and P53- cancers were also noted for former smokers compared to never smokers, but not for current smokers. Smoking status was established by questionnaire: exposure to ETS was identified dichotomously according to whether the respondent currently lived with a smoker. The positive finding with long-term smoking for one category of tumors is an interesting parallel to the recent result reported by Reynolds et al. (2004) and described in the updated document. Other results for associations between tobacco smoke exposures and either type of tumor are non-positive or equivocal, and may reflect partly the inadequate basis for identification of lifetime passive smoking, and also perhaps the compromises imposed by the prime intent of the study, which was to seek differential impacts on P53+ and P53- tumors. In contrast, 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.

References 22 and 23 are to the published abstracts of posters that were presented at the Annual Meeting of the Society for Epidemiological Research. Unfortunately the level of detail in these brief abstracts is quite sparse, and OEHHA has not been able to identify any subsequent major publications describing these studies. However the results presented are of interest and will be

added to the updated report, although they cannot be given the same weight as those described in detail in full papers. OEHHA is grateful to Mr. Lee for drawing our attention to these abstracts.

Rookus et al. (2000) described their analysis of a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smoking were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or if someone smoked daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. When passive smokers were excluded from the reference group, the risk of breast cancer among passive smokers was increased (OR: 1.2, 95% CI: 0.8-1.7). This risk was comparable to the risks of current smokers and ex-smokers relative to non-exposed controls (OR: 1.2, 95% CI:0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). Differential effects of passive exposure before first pregnancy or on P53 over-expression were not detected. This study is of interest in that ETS exposure from both domestic and occupational situations was measured, and directly it addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for. The authors state:

> "In conclusion: passive smoking seems to slightly increase the risk of breast cancer comparable to the risk increase following active smoking. Therefore, in studies on active smoking and breast cancer risk, the risk estimates will be biased to zero if passive smokers are included in the reference group."

This study is also of interest in that, in common with some others (e.g. Millikan et al., 1998; Manjer et al., 2001; Egan et al., 2002; Furberg et al., 2002) a statistically significant positive result was obtained for ex-smokers even where data for similar groups of current smokers failed to unequivocally demonstrate such an effect. Interpretation of this otherwise unexplained result may be aided by consideration of the hypothesized short-term anti-estrogenic effect of current smoking, and also of the issues of exposure timing during adolescence and young adulthood, which are elaborated in the OEHHA document.

Woo et al. (2000) described a population-based, nested case-control study in Washington County, MD. In 1975, the smoking status of adult household members was determined by census. Incident breast cancer cases (n = 706) during the subsequent 17 years were identified among women census participants through the Washington County Cancer Registry, along with age matched controls (n = 1,426). For all never active smokers, passive smoke exposure was not associated with breast cancer overall (odds ratio (OR)=1.04, 95% confidence interval (CI) 0.83-1.33). This was also true for postmenopausal never smokers (OR = 0.91, 95% CI 0.71-1.18). (Postmenopausal was defined as age >=50 years; it is assumed that this refers to age at diagnosis although the report does not state this explicitly.) However, there was a significantly elevated risk of breast cancer in premenopausal never-smoking women exposed to ETS, relative to those not exposed (OR = 2.78, 95% CI 1.37 – 5.63). Determination of ETS exposure status appears from the limited report to have been on the basis of cohabitation with a smoker at the time of the census. As noted elsewhere, this ignores other ETS exposure situations (e.g.

occupational) that are significant for many study populations, and also does not provide information on age or parity at the time of exposure. No efforts to control for confounding factors are described. In spite of these limitations of the study, and its very brief reporting, it clearly shows, as noted by the authors, an association between ETS exposure and premenopausal breast cancer, although the overall result for all cases (pre- and post-menopausal) is nonpositive. It is not clear from the report whether this difference actually relates to different response according to menopausal status at the time of diagnosis, or whether in fact the key variable is age and/or duration of exposure.

Comment 28:

7.4.2 Stomach cancer and ETS

Two relevant studies have been missed.[17,24] The evidence is not suggestive of a relationship.[6]

Response:

Reference 17 (Jee et al., 1999) is described, and referenced for other site-specific findings, elsewhere in the chapter. The result for stomach cancers will also be noted in the revised document.

Reference 24 (Hirayama, 1984) is extensively discussed in OEHHA (1997). The findings and earlier analysis are briefly referenced in section 7.4.2.1 of the present document. Both OEHHA (1997) and the present document found the evidence for an association between ETS exposure and stomach cancer to be inconclusive.

Comment 29:

7.4.3 Brain cancer in adults and ETS

Two relevant studies have been missed.[25,26] The overall evidence is inconclusive.[6]

Response:

These two reports (Hurley et al., 1996; Blowers et al., 1997) will be noted in the revised document: as the commenter points out, they do not impact the existing conclusion.

Comment 30:

7.4.4 Leukemia in adults and ETS

One relevant study has been missed.[27] It showed no association.

7.4.5 Lymphoma in adults and ETS

One relevant study has been missed.[27] It showed no association.

Response:

Reference 27 (Hirayama, 1987) is a review and meta-analysis of other data reported by this author, which were extensively described and evaluated in OEHHA 1997 based on the original published reports. The present report has concentrated similarly on original reports of studies as opposed to reviews, and also specifically on those publications which have appeared since the publication of OEHHA (1997).

Comment 31:

Other cancers in adults and ETS

As my review[6] demonstrates, there are also some limited data for a range of other cancers.

Response:

OEHHA did not find that any of these results was sufficiently convincing to impact the overall aim of the document, which is to improve and protect public health. However, we appreciate the commentator's review of these data, and will continue to monitor the scientific literature for any further results of interest.

Part B Chapter 8. Cardiovascular health effects

Introduction:

I disagree with the Draft's conclusions about ETS and heart disease for reasons that are discussed briefly in the enclosed unpublished review[28] which is concerned mainly with the epidemiological evidence, and at more length in an earlier published review,[29] which deals with both the experimental and the epidemiological evidence.

As my unpublished review[28] makes clear, there are a number of papers on the epidemiology of ETS and heart disease that appear to have been missed in the Draft. There are four published after 1997 that are relevant.[30-33]

The Draft would improve from having some up-to-date meta-analyses. These are given in an enclosed document.[14]

Comment 32:

As for lung cancer, heart disease studies published in recent years show a weaker relationship of risk to smoking by the spouse than previously published studies. It is notable that the relative risks from the two largest US studies, published in 1995 and 2003, were very close to 1.00 in each sex, and not statistically significant. These studies provide data on a total of over 20,000 heart disease cases, greater than the total number in all the other studies combined.

Response:

The comment does not specify the studies to which it refers, however, the following three studies fit the description of size and publication dates: LeVois and Layard, 1995; Layard, 1995; Enstrom and Kabat, 2003. There were concerns regarding exposure misclassification in both the exposed and control groups in these studies. LeVois and Layard included ex-smoking spouses in the exposed group as though they had smoked for the duration of the study period. In Layard's study, there was substantial difference in age at death between case and control groups, with cases 6-7 years older on average. Since age is a known CHD risk factor, the case and control groups would not have experienced the same age-related risks. The controls might have developed CHD had they lived as long as the cases; this could substantially affect the relative risk estimates. 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. In these three studies, the control groups were likely to have contained individuals exposed to ETS thus minimizing the chances of detecting any effect.

Comment 33:

While the overall adjusted relative risk estimates for spousal smoking are statistically significant, they are based on heterogeneous estimates which are substantially higher in small than in large studies. Many of the studies failed to control adequately for confounding or the various other sources of bias present in such epidemiological studies, with none adjusting for misclassification of smoking habits. Heart disease studies show no clearly significant relationship with workplace ETS exposure.

Response:

As regards control for confounding, no epidemiological study is perfect, but the data taken together demonstrate consistency of effect. In the He et al. (1999) meta-analysis described on p. 8-8, the pooled risk estimate from the 10 studies with better control for confounding (1.26; 95% CI 1.16-1.38) was not much different than the risk estimate from all 18 studies indicating that confounding effects were likely minimal.

OEHHA disagrees with the statement on workplace ETS exposure studies. Wells' 1998 meta-analysis of 8 studies of workplace ETS found significant association between exposure and CHD, with higher combined estimates from the studies that had better ETS exposure estimates and better confounding control.

Comment 34:

Again, claims that the epidemiological data for heart disease support an inference of causality[19,20] cannot be convincingly justified.[21]

Response:

The epidemiological data from a number of studies and meta-analyses alone indicate a statistically significant association of workplace and/or home ETS exposure with CHD (see draft Chapter 8). In addition, the inference of causality is supported by studies documenting adverse changes in heart disease-related endpoints after ETS exposure including loss of arterial elasticity (Stefanadis et al., 1998) and function (Otsuka et al., 2001; Raitakari et al., 1999; Sumida et al., 1998). The loss of arterial elasticity following 5 minutes of ETS exposure (as measured by changes in distensibility) was similar to the loss after 5 minutes of active smoking, 21% vs 27% (Stefanadis et al., 1998). Otsuka et al. (2001) reported decreased coronary flow velocity reserve (CFVR) after ETS exposure. In patients with angina, a CFVR of <2 was reported by Chamuleau et al. (2002) to be a significant predictor of coronary events, such as MI and death, in the year following testing. Thus ETS exposure is associated with several negative cardiovascular effects, many of which are also observed with active smoking.

References Used in the Comments

1. Lee PN. Uses and abuses of cotinine as a marker of tobacco smoke exposure. In: Gorrod JW, Jacob P, III, editors. Analytical determination of nicotine and related compounds and their metabolites. Amsterdam: Elsevier, 1999;669-719.

2. Lee PN. ETS and birthweight. 2003. www.pnlee.co.uk

3. Lee PN. ETS and sudden infant death syndrome. 2002. www.pnlee.co.uk

4. Thornton AJ, Lee PN. Parental smoking and risk of childhood cancer: a review of the evidence. Indoor Built Environ 1998;7:65-86.

5. Lee PN. Environmental tobacco smoke and cancer of sites other than the lung in adult non-smokers. Food Chem Toxicol 2002;40:747-66.

6. Lee PN. Epidemiological evidence on environmental tobacco smoke and cancers other than the lung. 2003. www.pnlee.co.uk

7. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, et al. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Control 2001;12:797-802.

8. Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. I. The dose-response relationship with amount and duration of smoking by the husband. Indoor Built Environ 2000;9:303-16.

9. Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. II. Adjustment for the potential confounding effects of fruit, vegetables, dietary fat and education. Indoor Built Environ 2001;10:20-39.

10. Lee PN, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. III. Adjustment for the biasing effect of misclassification of smoking habits. Indoor Built Environ 2001;10:384-98.

11. Lee PN, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. IV. Investigating heterogeneity between studies. Indoor Built Environ 2002;11:4-17.

12. Lee PN, Fry JS, Forey BA. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. V. Overall conclusions. Indoor Built Environ 2002;11:59-82.

13. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980-8.

14. Lee PN. Meta-analyses of the epidemiological evidence relating ETS to lung cancer and heart disease. 2004. www.pnlee.co.uk

15. Lee PN. Epidemiological evidence on environmental tobacco smoke and lung cancer. 2004. www.pnlee.co.uk

16. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. Int J Cancer 1990;45:1033-9.

17. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. Int J Epidemiol 1999;28:824-8.

18. Zeegers MPA, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). Cancer Causes Control 2002;13:83-90.

19. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58515 women with breast cancer and 95067 women without the disease. Br J Cancer 2002;87:1234-45.

20. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. Jpn J Cancer Res 1996;87:1001-9.

21. Furberg H, Millikan RC, Geradts J, Gammon MD, Dressler LG, Ambrosone CB, et al. Environmental factors in relation to breast cancer characterized by p53 protein expression. Cancer Epidemiol Biomarkers Prev 2002;11:829-35.

22. Rookus MA, Verloop J, de Vries F, van der Kooy K, Van Leeuwen FE. Passive and active smoking and the risk of breast cancer [Abstract (SER)]. Am J Epidemiol 2000;151(Suppl):S28.

23. Woo C, Davis D, Gravitt P, Skinner H, Ward C, White JE, et al. A prospective study of passive cigarette smoke exposure and breast cancer [Abstract (SER)]. Am J Epidemiol 2000;151(Suppl):S72.

24. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 1984;13:680-90.

25. Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. J Epidemiol Community Health 1996;50:442-6.

26. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). Cancer Causes Control 1997;8:5-12.

27. Hirayama T. Passive smoking and cancer: an epidemiological review. GANN Monograph on Cancer Research 1987;33:127-35.

28. Lee PN. Epidemiological evidence on environmental tobacco smoke and heart disease. 2004. www.pnlee.co.uk

29. Lee PN, Roe FJC. Environmental tobacco smoke exposure and heart disease: a critique of the claims of Glantz and Parmley. Hum Ecol Risk Ass 1999;5:171-218.

30. McElduff P, Dobson AJ, Jackson R, Beaglehole R, Heller RF, Lay-Yee R. Coronary events and exposure to environmental tobacco smoke: a case-control study from Australia and New Zealand. Tob Control 1998;7:41-6.

31. Iribarren C, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 2001;55:721-8.

32. Pitsavos C, Panagiotakos DB, Chrysohoou C, Tzioumis K, Papaioannou I, Stefanadis C, et al. Association between passive cigarette smoking and the risk of developing acute coronary syndromes: the CARDIO2000 study. Heart Vessels 2002;16:127-30.

33. Chen R, Tunstall-Pedoe H. Coronary heart disease in relation to passive smoking by self report, serum cotinine and their combination: Scottish MONICA study [Abstract]. Society for Epidemiologic Research 36th Annual Meeting, Atlanta, Georgia, June 11-14, 2003. Am J Epidemiol 2003;157(Suppl):S27.

References used in responses:

Ahluwalia IB, Grummer-Strawn L, Scanlon KS (1997). Exposure to environmental tobacco smoke and birth outcome: Increased effects on pregnant women aged 30 years or older. Am. J. Epidemiol. 146:42-7.

Anderson HR, Cook DG (1997). Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. Thorax 52(11):1003-9.Lee reviewed 956.

Armstrong R, Imrey P, Lye M, Armstrong M, Yu M, Sani S (2000). Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Int J Epidemiol 29:991-8.

Blowers L, Preston-Martin S, Mack WJ (1997). Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). Cancer Causes Control 8(1):5-12.

Chamuleau SA, Tio RA, de Cock CC, de Muinck ED, Pijls NH, van Eck-Smit BL, et al. (2002). Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol 39(5):852-8.

Conway K, Edmiston SN, Cui L, Drouin SS, Pang J, He M, Tse CK, Geradts J, Dressler L, Liu ET, Millikan R, Newman B. (2002) Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. Cancer Res. Apr 1;62(7):1987-95.

Dejmek, J.; Solansk, y. I; Podrazilova, K., and Sram, R. J. (2002). The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. Environ Health Perspect. 110(6):601-6.

Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, et al. (2002). Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. Epidemiology 13(2):138-45.

Enstrom JE, Kabat GC (2003). Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. BMJ 326(7398):1057

Furberg H, Millikan RC, Geradts J, Gammon MD, Dressler LG, Ambrosone CB, et al. (2002). Environmental factors in relation to breast cancer characterized by p53 protein expression. Cancer Epidemiol Biomarkers Prev 11(9):829-35.

He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK (1999). Passive smoking and the risk of coronary heart disease--a meta-analysis of epidemiologic studies. N Engl J Med 340(12):920-6.

Hirayama T (1984). Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13(6):680-90.

Hirayama T. Passive smoking and cancer: an epidemiological review. GANN Monograph on Cancer Research 1987;33:127-35. As cited in Cal/EPA (1997).

Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, et al. (1995). A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. Jpn J Cancer Res 86(2):146-54.

Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. (1996). Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. Jpn J Cancer Res 87(9):1001-9.

Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG (1996). Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. J Epidemiol Community Health 50(4):442-6.

Jaakkola JJ, Jaakkola N, Zahlsen K (2001). Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. Environ Health Perspect 109(6):557-61.

Jee SH, Ohrr H, Kim IS (1999). Effects of husbands' smoking on the incidence of lung cancer in Korean women. Int J Epidemiol 28(5):824-8.

Kharrazi M, DeLorenze GN, Kaufman FL, Eskenazi B, Bernert JT, Graham S, et al. (2004). Influence of low level environmental tobacco smoke on pregnancy outcomes. Epidemiol. In press.

Kinney, H. C.; Filiano, J. J.; Sleeper, L. A.; Mandell, F.; Valdes-Dapena, M., and White, W. F. (1995). Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. Science 269(5229):1446-50.

Klonoff-Cohen HS, Edelstein SL, Lefkowitz ES, Srinivasan IP, Kaegi D, Chang JC, et al. (1995). The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. JAMA 273(10):795-8.

Layard MW (1995). Ischemic heart disease and spousal smoking in the National Mortality Followback Survey. Regul Toxicol Pharmacol 21(1):180-3.

LeVois ME, Layard MW (1995). Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. Regul Toxicol Pharmacol 21(1):184-91 (REF: 55).

Manjer J, Malina J, Berglund G, Bondeson L, Garne JP, Janzon L (2001). Smoking associated with hormone receptor negative breast cancer. Int J Cancer 91(4):580-4.

Millikan RC, Pittman GS, Newman B, Tse CJ, Selmin O, B R, et al. (1998). Cigarette smoking, N-acetyltransferase 1 and 2, and breast cancer risk. Cancer Epidemiology, Biomarkers & Prevention 7(5):371-78.

Navarro HA, Mills E, Seidler FJ, Baker FE, Lappi SE, Tayyeb MI, et al. (1990). Prenatal nicotine exposure impairs beta-adrenergic function: persistent chronotropic subsensitivity despite recovery from deficits in receptor binding. Brain Res Bull 25(2):233-7.

Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, et al. (2001). Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Control 12(9):797-802.

Otsuka R, Watanabe H, Hirata K, Tokai K, Muro T, Yoshiyama M, et al. (2001). Acute effects of passive smoking on the coronary circulation in healthy young adults. JAMA 286(4):436-41.

Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Celermajer DS (1999). Arterial endothelial dysfunction related to passive smoking is potentially reversible in healthy young adults. Ann Intern Med 130(7):578-81.

Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, et al. (2004). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. J Natl Cancer Inst 96(1):29-37.

Rookus M, Verloop J, de Vries F, van der Kooy K, van Leeuwen F (2000). Passive and active smoking and the risk of breast cancer. 151. 151(11):S28.

Slotkin TA, Epps TA, Stenger ML, Sawyer KJ, Seidler FJ (1999). Cholinergic receptors in heart and brainstem of rats exposed to nicotine during development: implications for hypoxia tolerance and perinatal mortality. Brain Res Dev Brain Res 113(1-2):1-12.

Stefanadis C, Vlachopoulos C, Tsiamis E, Diamantopoulos L, Toutouzas K, Giatrakos N, et al. (1998). Unfavorable effects of passive smoking on aortic function in men. Ann Intern Med 128(6):426-34.

Sumida H, Watanabe H, Kugiyama K, Ohgushi M, Matsumura T, Yasue H (1998). Does passive smoking impair endothelium-dependent coronary artery dilation in women? J Am Coll Cardiol 31(4):811-5.

Wang X, Tager IB, Van Vunakis H, Speizer FE, Hanrahan JP (1997). Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. Int J Epidemiol 26(5):978-88.

Wells AJ (1998). Heart disease from passive smoking in the workplace. J Am Coll Cardiol 31(1):1-9.

Windham GC, Hopkins B, Fenster L, Swan SH (2000). Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 11(4):427-33.

Woo KS, Chook P, Leong HC, Huang XS, Celermajer DS (2000). The impact of heavy passive smoking on arterial endothelial function in modernized Chinese. J Am Coll Cardiol 36(4):1228-32.

Yuan J-M, Wang W-L, Xiang Y-B, Gao Y-T, Ross R, Yu M (2000). Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. Int J Cancer 85:364-9.

Zeegers MP, Goldbohm RA, van den Brandt PA (2002). A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). Cancer Causes Control 13(1):83-90.

Zhu K, Levine RS, Brann EA, Hall HI, Caplan LS, Gnepp DR (2002). Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Cancer. 99(1):119-23.

Comments of R.J. Reynolds Tobacco Company ("RJRT")

Comment 1:

The current California Environmental Protection Agency 2003 Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant," ("2003 Draft Report") does not support designation of environmental tobacco smoke ("ETS") as a toxic air contaminant ("TAC") in California. Additionally, the 2003 Draft Report reaches conclusions regarding ETS and breast cancer that are not supported by the record.[5] Furthermore, new data on ETS and breast cancer published since the 2003 Draft Report must be considered before a final Report is issued.

Response:

We address these general comments below in response to specific comments. Additional material, which has appeared in the literature since the appearance of the 2003 draft, has been reviewed and is described and evaluated in the latest version of the report.

Comment 2:

The 2003 Draft Report Does Not Comply with the Statutory Requirements Pertaining to Designating a Substance as a TAC

The California Environmental Protection Agency's ("Cal/EPA") authority to designate a substance as a TAC is not absolute. Specifically, Sections 39650-39674 of the California Health & Safety Code set forth several requirements that the Agency must meet before designating a substance as a TAC. For example, Section 39660 initially requires Cal/EPA generally to assess the exposure[6] and health effects[7] data for the substance and to specifically determine whether

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[5] Prior to the publication of the California Environmental Protection Agency's ("Cal/EPA" or "Agency") 1997 Report on ETS, RJRT submitted extensive comments to Cal/EPA explaining the basis for RJRT's disagreement with Cal/EPA's conclusions regarding ETS and health. Most of these comments were either rejected or ignored by Cal/EPA. Although RJRT stands by its previously submitted comments, those comments will not be revisited in this letter. Rather, this letter will focus on two issues that are specific to the 2003 Draft Report and thus not addressed in any previous comments by RJRT: 1) the failure of the current Draft Report to meet the requirements set forth in the California Statutes for designation of ETS as a TAC; and 2) the current Draft Report's causal conclusions regarding ETS and breast cancer.

[6] With respect to the ETS exposure assessment contained in the 2003 Draft Report, RJRT has retained Dr. Roger Jenkins to provide comments to Cal/EPA. Dr. Jenkins is a Group Leader and Distinguished R&D Staff Member at Oak Ridge National Laboratories. He has conducted and

current California ETS exposures are responsible for adverse health effects. If the Agency determines that current California ETS exposures are responsible for adverse health effects, then Section 39660 requires Cal/EPA to provide an estimate of the exposure level that may cause or contribute to adverse health effects in California, i.e., a California-specific risk assessment:

> (2) The evaluation shall also contain an estimate of the levels of exposure that may cause or contribute to adverse health effects. If it can be established that a threshold of adverse health effects exists, the estimate shall include both of the following factors:
>
> (A) The exposure level below which no adverse health effects are anticipated.
>
> (B) An ample margin of safety that accounts for the variable effects that heterogeneous human populations exposed to the substance under evaluation may experience, the uncertainties associated with the applicability of the data to human beings, and the completeness and quality of the information available on potential human exposure to the substance. In cases in which there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposure to the substance.

Cal. Health and Safety Code § 39660(2)

The 2003 Draft Report is completely devoid of any legitimate attempt to comply with these requirements. Assuming *arguendo* that the 2003 Draft Report has reached appropriate conclusions regarding ETS exposures and general health effects, the Report has not "estimated the levels of exposure [in California] that may be responsible for adverse health effects" in California. Moreover, the Report does not express any opinion regarding the existence or non-existence of a threshold level for ETS.

Rather than complying with the specific requirements set forth in § 39660(2), the Report employs an overly simplistic and wholly inappropriate approach to attempt to link ETS exposures with specific incidents of disease in California by utilizing the statistical concept of attributable risk[8] First and foremost, the use of attributable risk calculations requires the underlying epidemiology to be scientifically accurate. For the reasons set forth in RJRT's prior submissions to Cal/EPA, RJRT submits that the underlying epidemiology suffers from

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published extensive research regarding ETS chemistry and exposures. Dr. Jenkins' comments are based solely on his own expertise in this area and not on any input from RJRT.

[7] With respect to the general health effects conclusions contained in the 2003 Draft Report, RJRT submitted extensive comments to Cal/EPA prior to the Agency's 1997 Report which explained the bases for RJRT's disagreement with these conclusions. Since the stated purpose of the 2003 Draft Report is to propose the listing of ETS as a TAC, RJRT will focus solely on the California-specific requirements set forth in Section 39660 which require the Agency to conduct a California-specific risk assessment for ETS.

[8] See Attributable Risk Table ES.2 on p. ES-11 and Table 1.2 on p.1-10.

substantial scientific inaccuracies which only magnify the inappropriateness of using these studies for attributable risk calculations.

Second, the relative risks used in the attributable risk calculations are not applicable to the California population. The 2003 Draft Report contains no explanation of how the relied upon epidemiology, even if scientifically accurate, has any relevance to the California-exposed population. The 2003 Draft Report takes great pride in distinguishing California ETS exposures as being substantially lower than the rest of the Country . [See ES-5, 6; IV-8, 9; Table IV-4] Thus, epidemiology studies conducted in other states (and even other countries) would necessarily be premised on populations with higher ETS exposures. Again, assuming *arguendo* that the relative risks from these studies are accurate, these studies provide only limited information about potential risks for the California-exposed population. Thus, using their relative risks for attributable risk calculations in California is wholly inappropriate.

Significantly, for at least three of the diseases that the 2003 Draft Report determined were causally associated with ETS, recent epidemiology studies based solely on California-exposed populations reported no causal association. In a prospective study of 118,094 Californians, Enstrom and Kabat concluded there was no causal association between ETS exposure and lung cancer or coronary heart disease[9]. James Enstrom subsequently petitioned the National Toxicology Program to delist ETS as a "known human carcinogen.."[10] Furthermore, in a 2004 study discussed in more detail later in these comments, Peggy Reynolds et al., prospectively followed 116,544 Californians and found no increased risk of breast cancer from ETS exposure[11].

Additionally, as correctly acknowledged in the 2003 Draft Report, these attributable risk calculations do not address whether there are risks from non-residential and non-workplace exposures in California. Since smoking is banned in practically all indoor environments in California other than in private homes and private automobiles, this omission renders the 2003 Draft Report useless for its stated purpose of determining whether current ETS exposures in California warrant designation of ETS as a TAC and future regulation of ETS in California.[12]

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[9] Enstrom, James E. and Kabat, Geoffrey C., Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98; BMJ, 326:1057-66 (2003). The study population was the California subset of the American Cancer Society cancer prevention study (CPS 1) that followed 1,078,894 adults from 25 states.

[10] See January 14, 2004, letter from James E. Enstrom to C.W. Jameson, Ph.D., of the National Toxicology Program. (Attached as "Exhibit A").

[11] Reynolds, Peggy, et a.1, Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, J. Natl. Cancer Inst., 96(1): 29-37 (2004).

[12] Although the Exposure chapters of the 2003 Draft Report spend substantial verbiage attempting to estimate exposure to ETS from sources other than residential and occupational

Finally, the flawed use of attributable risk calculations cannot be cured by developing better attributable risk calculations. The simplistic use of attributable risk calculations, regardless of the quality of those calculations, is not appropriate for meeting the requirements set forth in Section 39660(c)(2). While RJRT stands by its belief that ETS exposures in residential and occupational environments do not cause adverse health effects in adult nonsmokers, that is not the relevant issue for purposes of determining whether the 2003 Draft Report complies with Section 39660(c)(2).

The relevant issue is whether current exposures in California warrant designation of ETS as a TAC and, if so, what are "the levels of exposure that may cause or contribute to adverse health effects [in California]." This issue cannot be evaluated by using attributable risk calculations. The epidemiology studies cited in the 2003 Draft Report do not analyze environments with exposures as low as those currently present in California. Even epidemiology studies that address past exposures in California may not be relevant for this purpose since the need for future regulation cannot be premised on exposure scenarios that no longer exist. Thus, the 2003 Draft Report does not comply with the statutory requirements set forth in Section 39660(c)(2).

Response:

OEHHA and ARB are advised by their respective legal counsels that the actions taken and proposed are appropriate. The intended purpose of the public comment period for the health effects document is to identify scientific issues in the report that may need further attention, rather than to debate any legal issues.

One issue, which OEHHA can address, is the comment that the attributable risk calculations are irrelevant for California. The comment fails to recognize that the lower smoking rates in California are factored into the calculations of attributable risk. There is no reason to believe that Californians would in fact not respond to ETS like other people, given the broad diversity of people present in California in terms of genetic, lifestyle, diet, and so forth.

Another issue is 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. 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

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settings, the attributable risk calculations in the 2003 Draft Report make absolutely no effort to characterize any potential risks from ETS exposure in these environments. Therefore, the Report fails to meet this fundamental requirement set forth in the California statutes and does not satisfy the statutory definition of a TAC.

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 3:

The 2003 Draft Report's Conclusions Regarding Active Smoking, ETS and Breast Cancer Are Not Supported by the Record

In 1997, Cal/EPA's Report on ETS examined four studies on ETS and breast cancer and determined there was insignificant evidence of a causal role[13]. Indeed, the 1997 Report did not even conclude that there was "suggestive evidence" of a causal association between ETS and breast cancer[14]. Now, six years later, after reviewing several new epidemiology studies with data remarkably similar to the four studies reviewed in the 1997 Report, the 2003 Draft Report

[13] 1997 Report, p. 7-44. Additionally, in 1997, the Cal/EPA Report referred to the alleged association between "active smoking" and breast cancer as "equivocal."

[14] 1997 Report, p. ES-2.

concludes that ETS exposure is causally associated with breast cancer. This reversal of conclusions is not justified by the record[15].

Response:

The availability of new data and analyses since 1997 is one of the reasons why this update was undertaken. It is because of these new data, coupled with more rigorous analyses of the older data and use of information from the toxicology literature on carcinogens found in tobacco smoke, that the different conclusion on breast cancer was reached in the present report.

Comment 4:

First, numerous public health agencies that have investigated the possible relationship between active smoking, ETS and breast cancer and reviewed the same data relied upon by Cal/EPA, have concluded that there is insufficient evidence of a causal role. Cal/EPA is the only one reaching a contrary conclusion[16].

The International Agency for Research on Cancer ("IARC"), the American Cancer Society ("ACS") and the National Cancer Institute ("NCI") all have evaluated the purported association between active smoking or ETS and breast cancer and concluded that the evidence is insufficient to link either smoking or ETS exposure with breast cancer. For example, in June 2002, IARC issued a press release on secondhand smoke carcinogenicity which stated "[c]oncern that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking [ETS] is unjustified by the evidence."[17]t3 After an extensive literature review on the subject, IARC concluded that the prospective studies "provide no support for a causal relation"

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[15] At RJRT's request, Sanford Barsky, M.D. has submitted his own analysis of the 2003 Draft Report's breast cancer discussion and the literature on ETS and breast cancer. Dr. Barsky is a Professor of Pathology at the UCLA School of Medicine with special interest in breast cancer and lung cancer. Dr. Barsky's comments are based solely on his own expertise in this area and not on any input from RJRT.

[16] Admittedly, RJRT has not always agreed with the conclusions of various public health agencies regarding the association between ETS and disease. In many instances, RJRT's disagreement is premised on the difference between reaching causal conclusions that are based on valid scientific considerations versus those conclusions that are adopted by public health agencies and organizations which appear to be based on the "better safe than sorry" philosophy. While RJRT does not believe that many causal conclusions regarding ETS are supported by the science, we do recognize that public health agencies sometimes have a different standard for reaching causal conclusions to communicate to the public and the media. Therefore, when such agencies have reviewed the data on ETS and a disease such as breast cancer and have publicly stated that the evidence is insufficient to reach causal conclusions, this is particularly compelling and persuasive evidence that the scientific standard for determining causality has not been met.

[17] See httpJ/www.iarc.fr/pageroot/PRELEASES/nr141a.html (Attached as "Exhibit B").

and added that the "lack of a positive dose-response argues against a causal interpretation."[18] The current ACS website on "What Causes Breast Cancer" does not list ETS among the "lifestyles" risk factors[19]. Furthermore, the ACS does not list active smoking as a risk factor and notes that a link between active smoking and breast cancer has not been found[20]. Likewise, the current NCI website on breast cancer risk factors ("Health Professional Version") does not include ETS or active smoking[21].

Response:

OEHHA values highly the assessments of IARC, NCI, and ACS. However, in undertaking evaluations of the scientific literature under our mandates for Toxic Air Contaminants, OEHHA makes an independent evaluation of the currently available data, and does not just follow without analysis the conclusions of other authorities. 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 that 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. In addition, the biological plausibility for an ETS link to breast cancer made in our analysis utilized information from the animal toxicology literature, which in our opinion has been given little consideration by these authorities (and epidemiologists in general).

Comment 5:

Second, well-respected epidemiologists in the public health community also have agreed that the evidence linking either smoking or ETS with breast cancer is insufficient to establish causality. For example, Jonathan Samet, M.D., senior scientific editor for the 2003 Surgeon General's report on active smoking and the Surgeon General's report on ETS that is currently being drafted[22], has stated that "investigation of cancer sites other than the lung should be guided by

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[18] See http://www-cie.iarc.fr/htdocs/monographs/vol83/02-involuntary.html section 5.2. (Attached as "Exhibit C").

[19] http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_breast_cancer_5.asp?sitearea=. Revised 10/02/03. (Attached as "Exhibit D")

[20] Id.

[21] See http://www.cancer.gov/cancerinfo/pdq/prevention/breast/healthprofessional/ - Section 175, Revised 2/20/04. (Attached as "Exhibit E")

[22] See the Johns Hopkins Bloomberg School of Public Health magazine, .http://www.jhsph.edu/Mag_Spring03/smokeout/expert.html. Additionally, on numerous occasions, Dr. Samet has served as an expert witness against the tobacco industry in smoking and health litigation.

the data from active smokers and by appropriate toxicological evidence."[23] Without scientific consensus that active smoking has a causal association with breast cancer, scientists agree it is biologically implausible that ETS is causally associated with breast cancer.[24]

Response:

Some well-respected experts disagree with OEHHA's present conclusions, others agree with them, as is evident (inter alia) from the other comments received on this document. In addition, the premise that if there is insufficient evidence to link active smoking with a disease, then it is less likely that passive smoking would be a risk factor for that disease, is based upon the assumption that ETS is chemically identical to mainstream smoke. As noted elsewhere in these comments and responses, this is not correct, and concentrations of some carcinogens in ETS are much higher than in mainstream smoke (see response to comment 13 from LeVois). Additionally, it assumes a linear dose-response and similar toxicological interactions among ETS constituent as occurs among mainstream smoke constituents. In fact, there is evidence that the response is not linear, and that active smoking is anti-estrogenic which would mask carcinogenic effects on breast tissue, complicating the relationship between active smoking and breast cancer.

Comment 6:

Contrary to the opinions of every major public health organization and many well-respected epidemiologists who have reviewed the scientific literature on ETS and breast cancer, the 2003 Draft Report concludes that the evidence is consistent with a causal association between ETS and breast cancer. However, the Draft contains numerous errors, several misinterpretations and, in many cases, simply fails to explain how it analyzed key studies. First, the bases for the conclusion are wholly unclear, as the Draft does not specify on which data and studies it truly relies. Second, and more important, the data as a whole discussed or cited in the Draft (plus additional data Cal/EPA must consider) does not support a conclusion that a causal association exists between breast cancer and ETS. And finally, because the Draft's conclusion that active smoking causes breast cancer is flawed, it is biologically implausible to conclude that ETS causes breast cancer.

Providing Cal/EPA with meaningful comments on the 2003 Draft Report's section on ETS and breast cancer is difficult because Cal/EPA does not clearly explain on which studies and data it relies. The Draft discusses or cites to approximately 16 new studies on ETS and breast cancer

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[23] Samet, J.M. and Wang, S.S, Environmental Toxicants: Human Exposures and Their Health Effects, Chapter 10 - Environmental Tobacco Smoke, (2°d ed. 2000), 319-375, 349. (Attached as "Exhibit F")

[24] Id.

published since the 1997 Report[25]. However, the Draft makes inconsistent references to the studies and inaccurate descriptions of the data. For example, Section 7.4.1.5 states that since its 1997 Report, "[f]our cohort and six case-control studies have reported on breast cancer risk and exposure to ETS."[26] The supporting parenthetical, however, cites a study on active smoking (Terry 2002)[27] and omits one of the cohort studies (Nishino 2001) that examines ETS and breast cancer risk[28]. Subsequently, in the section titled "Strength and Specificity," the 2003 Draft Report states "three new cohort studies ... reviewed for this update did not provide evidence of an association between ETS exposure and breast cancer risk....,,"[29] Once again, the Nishino cohort study is not included in the parenthetical. Does Cal/EPA rely on three cohort studies or four? Why is the Nishino study not cited with the other cohort studies? Why does the Nishino study receive only cursory discussion later in the section? These Nishino study omissions and the Draft's failure to explain the Nishino study's role in the analysis are especially troubling since Nishino is a statistically significant study showing a protective effect[30]. This type of inconsistency makes it impossible to determine what data Cal/EPA finds convincing enough to conclude a casual relationship exists between ETS and breast cancer.

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[25] See Tables 7.4 E-M, pp. 7-122, 7-137: A precise determination of the number of studies considered in this section of the 2003 Draft Report is difficult since there is inconsistency between studies discussed and those listed in the various Tables. Note, for example, that the Marcus 2000 study is listed in Table 7.41 and two Morabia studies (1998, 2000) are listed in Table 7.4K, but they are not listed in Tables 7.4E or F. The Lui 2000 study is listed in Table 7.4E but not in 7.4F.

[26] Draft Report, p. 7-122.

[27] Terry, 2002. Interestingly, the Terry study observed a risk of breast cancer primarily in women who smoked 40 years or more. Little or no increased risk was observed in women who smoked less than 30 years. (pp. 724, 726). It is biologically implausible that exposure to ETS increases the risk of breast cancer if direct smoking of 30 years or less does not.

[28] The Draft Report does briefly discuss the Nishino study later in the ETS section (p. 7-129), but why it fails to cite this study (twice) when listing cohort studies examining ETS and breast cancer risk is unclear. Thus, what weight, if any, Cal/EPA places on the Nishino cohort study in concluding that ETS causes breast cancer is uncertain. Interestingly, Cal/EPA's brief discussion of the Nishino study states, without further analysis, that the relative risk and confidence intervals are as follows: 0.58 relative risk, 95% confidence interval 0.34-0.99. Cal/EPA does not acknowledge that these results show a statistically significant protective effect of ETS on breast cancer. Furthermore, Table 7.4F incorrectly lists the Nishino as a statistically insignificant study with a confidence interval of 0.32-1.1. This type of inaccuracy is troubling and casts doubt on the reliability of Cal/EPA's analysis and conclusions.

[29] Jee 1999, Wartenberg 2000 and Egan 2002 in parenthetical.

[30] RJRT does not contend that the results of this study warrant a conclusion that ETS reduces breast cancer risk. Rather, this study - in combination with all other studies - further demonstrates that Cal/EPA's conclusions regarding ETS and breast cancer are not supported by the scientific literature.

Response

This comment appears to consist primarily of statements that the commentator found the document unclear or hard to understand, as well as general disagreement with our conclusion regarding an association between ETS and breast cancer. In reply, OEHHA notes the commentator's disagreement, but does not find any specific arguments here that would lead to modification of the report's conclusion. Some specific instances where extended explanations or improved descriptions are needed in the report have been identified as a result of these and other comments, and the draft report is being revised to address these. It is regrettable that the commentator found the report hard to follow, and we hope our revisions make the document clearer.

The document discusses Nishino, albeit briefly and does include it in Tables 7.4 E, 7.4F, and 7.4L. We did not ignore this study and do note in the text the presence of an inverse relationship between ETS exposure and breast cancer risk in the study. Furthermore, the data are included in the summary statistics presented in the conclusion. This study unfortunately relied only on one question at baseline to ascertain exposure, and was likely to have missed significant other sources of exposure, as noted in Table 7.4F. The authors note in their discussion "In this study, women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoke exposure…". In regards to drawing conclusions based on these findings the authors state, "The relationship between passive smoking and breast cancer in this study should be interpreted with caution." Thank you for drawing attention to a typographic error in the text in regards to the confidence intervals. The confidence intervals for the study in the text should match those given in the tables 7.4F and 7.4L; 0.58 (CI 0.32-1.1). These are for the relative risk of breast cancer for non –smoking women whose husbands smoke adjusted for confounding variables (table 4 in Nishino et al, 2001). The significant data that are mentioned in your footnote are only adjusted for age and should not be used. In general, in this study adjusting for confounding did not make a difference in the results except for breast cancer; as you rightly point out, adjustment for age alone results in a statistically significant finding. However, adjustment for additional confounders moves the RR into a statistically non-significant category.

Given the difficulties in epidemiological studies, particularly with exposure ascertainment for ETS, it is not surprising that one of the many studies conducted would come up with an inverse relationship. The majority of studies show either null results or elevated risks.

Comment 7:

Furthermore, the "Summary of Risk Estimates" section discusses a review by Kenneth Johnson of 15 published studies and the summary risk estimates reached in this review. However, the Johnson review is "submitted" and is unavailable for independent analysis[31]. Thus, the methodology Johnson used in arriving at these risk estimates is unclear. Nor is it clear how much weight Cal/EPA places on Johnson's review. While the studies included in the Johnson review and the summary risk estimates are listed in Tables 7.4E-G (the first three tables in the Draft listing ETS studies), Tables 7.4H-M contain some studies not included in Tables 7.4E-G (and, thus, apparently not included in Johnson's review). The importance placed on Johnson's review and on all other studies and data must be more clearly explained before RJRT or any member of the public can provide adequate and meaningful comment.[32]

Response:

In response to this comment and others, we have added more detail on the analysis, and have included more studies. This revised meta-analysis is presented in the revised report. Since this analysis is not primary research, and since all of the data utilized are presented in the original papers or in explanatory letters to the editor subsequent to publication, the analysis can be replicated by anyone using standard statistical techniques. The results of this exercise are used to give a quantitative assessment to the general qualitative impression generated by the contributions of mechanistic, toxicologic, and epidemiologic data supporting the role of ETS in causation of breast cancer.

Comment 8:

The difficulty in providing meaningful comment regarding Cal/EPA's analysis and methodology is compounded by the fact that the referenced studies provide no basis for Cal/EPA to change the conclusion reached in the Agency's 1997 Report, i.e., that there is insufficient evidence of a causal association between ETS exposure and breast cancer. For example, none of the studies reviewed in the 1997 Report show a relative risk point estimate equal to or below 1.0, but three of the studies since 1997 report relative risks equal to or below 1.0.[33] Of the remaining 13 new

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[31] 2003 Draft Report, p. 7-140. A PubMed search identified no Kenneth Johnson review on ETS or breast cancer published in 2003-04.

[32] Because of these concerns regarding the bases for Cal/EPA's conclusions in the 2003 Draft Report, RJRT requests an opportunity to comment again on the revised draft report if Cal/EPA does not change its conclusion that a causal association exists between ETS and breast cancer.

[33] Wartenberg, 2000, Nishino, 2001 and Lash, 2002. Furthermore, Wartenberg and Nishino are prospective studies. The Wartenberg study, funded by the U.S. Environmental Protection Agency among others, followed over 146,000 women prospectively and finds no association between ETS exposure and breast cancer death. The 2001 Nishino study followed 9,675 women

studies, more than half are not statistically significant[34]. 30 Thus, if anything, there is less scientific basis in 2003 to conclude that ETS is causally associated with breast cancer.

Cal/EPA tries to explain away the inconsistency between its 2003 breast cancer conclusion and the scientific data by arguing that some studies failed to include childhood or occupational ETS exposure with spousal exposure, resulting in artificially lower relative risk findings[35]. However, Daniel Wartenberg replied to criticism that his study failed to include occupational exposure risks by stating his data showed no increased risk at work, at other locations, or all sources combined[36]. Moreover, the authors of the most recent study that includes childhood exposure in its analysis question the importance of childhood ETS exposure in breast cancer development[37] 33 Finally, IARC, ACS and NCI considered these same studies and do not differentiate between studies looking at only spousal exposure and those including childhood or occupational exposure. Cal/EPA appears to be making an arbitrary distinction for breast cancer that other scientific organizations looking at ETS and breast cancer risk fail to make.

Finally, the 2003 Draft Report's summary paragraph (p. 7-147) calls into question Cal/EPA's analysis of the data and bases for its conclusion by claiming that "in comparison to studies reviewed in the previous OEHHA report (Cal/EPA 1997), current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk..." (emphasis added). This statement is false. In 1997, four studies were evaluated, all of which had relative risks over 1.0. Two of those four studies had relative risks over 2.0. The 2003 Draft Report evaluated several more studies. Looking at Table 7.4F from the Johnson review, three of the 11 new studies have relative risks of 1.0 or lower, and all three are recent, large prospective studies. Seven of the 11 studies are statistically insignificant. In reality, the 2003 Draft Report shows that the data considered in 1997 was more indicative of an association than the data presented in studies since 1997. The data in the Draft, considered as a whole, is substantially less indicative of a positive association between breast cancer and ETS exposure.

In addition to its ETS analysis, Cal/EPA also concludes in the 2003 Draft Report that a causal association exists between active smoking and breast cancer. The Draft only addresses direct smoking for biological plausibility, apparently in attempt to bolster an otherwise weak

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prospectively and actually reports a statistically significant reduced risk of breast cancer among women exposed to ETS, as previously discussed.

[34] See Tables 7.4F and 7.41. Interestingly, the percentage of statistically significant vs. statistically insignificant studies is almost identical to the percentage in the 1997 Report, where half of the studies were statistically significant and half were not.

[35] See Report, pp. 7-128-30; 7-140; 7-147; Tables 7.4 F, 7.4 E.

[36] Draft Report, p. 7-128, citing Wartenberg 2001.

[37] Kropp, p. 522. "Contrary to the assumption that breast tissue is more susceptible to carcinogens at young ages, early passive smoking may not play an important role in breast carcinogenesis."

conclusion regarding ETS and breast cancer. Otherwise, this determination has no bearing on ETS as a TAC. RJRT disagrees with the Agency's conclusion that there is a causal association between active smoking and breast cancer.[38]

Response:

There are a number of new studies that do show significantly elevated risks particularly when exposure ascertainment was relatively better. In addition, the meta-analysis conducted with Johnson in our report (revised with additional studies added), demonstrates significantly elevated risks. Although many of the new studies did not necessarily indicate statistically significant elevations considered in isolation, most had point estimates above one and several indicated significant trend tests for elevated risk with a number of different metrics of exposure. Thus, we believe that taken together the older and newer studies, when analyzed thoroughly for better exposure ascertainment, and utilizing meta-analytic techniques provide evidence that ETS exposure is associated with breast cancer.

Due to the difficulties of ascertaining exposure to ETS in epidemiological studies, OEHHA sought to distinguish studies on the basis of how exposure was ascertained. The better the exposure (including questions not just about home, or work, or childhood, but about all environments, for example), the stronger the evidence for an association. This in itself provides evidence that there is an association. As noted here and elsewhere, although large prospective studies are often preferred over case-control studies, if the exposure assessment is poor, one does not necessarily gain a better understanding of causal associations relative to other study designs where the exposure assessment is better.

Comment 9:

The 2003 Draft Report's Conclusions Regarding ETS and Breast Cancer Are Not Supported by More Recent Studies on ETS, Breast Cancer and Californians

Additional data published since the release of the 2003 Draft Report further supports the conclusion that there is insufficient evidence that ETS is not causally associated with breast cancer. The Board must consider "all available scientific data" in determining whether a

[38] As discussed in the text above, a conclusion that active smoking is causally related to breast cancer is not consistent with the weight of the scientific evidence. Tables 7.4A&B list studies reviewed on direct smoking and breast cancer. The Tables demonstrate inconsistencies among the studies between the reported risks of breast cancer, and many studies lack statistically significant increased risks.

substance is a TAC[39]. On January 7, 2004, a new study was published examining breast cancer risk from active smoking and ETS exposure. See Reynolds, Peggy, et al., Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, J. NatI. Cancer Inst.; 96(1): 29-37 (2004) ("Reynolds study"). (Attached as "Exhibit G"). Obviously, the Agency staff was unable to consider the Reynolds study in preparing the draft Report since the study was not published until after November 2003. Therefore, the 2004 Reynolds study is not included in the Report. Nonetheless, under California law, it must be considered before a final report is issued for consideration by the Board.

The Reynolds study is particularly pertinent to a Californian's risk of developing breast cancer from ETS. The Reynolds study population consists entirely of Californians - a large, prospectively-followed cohort of female professional school employees from the California Teachers Study[40]. Studies have shown that breast cancer incidence varies from one geographic area to another[41]. No other study included in the 2003 Report involves a population of California cancer subjects. Thus, a study population consisting entirely of Californians has significant bearing on the risk Californians face of developing breast cancer from ETS exposure.

The Reynolds study "found no evidence of a relationship between household passive smoking exposure and breast cancer risk[42]. The hazard ratios for developing breast cancer from household ETS exposure were "close to unity for all passive smoking exposure categories examined." The hazard ratios ranged from .87 to 1.01 and were not statistically significant[43].

The Reynolds study is consistent with the four previous prospective studies that failed to find a statistically significant increased risk of breast cancer from ETS. Therefore, the five large prospective studies conducted since Cal/EPA's 1997 Report reach consistent results, and one study even reports a statistically significant protective effect from ETS. Moreover, these studies,

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[39] See Cal Health & Safety Code §§ 39650, 39660. The California legislature determined that "the identification and regulation of toxic air contaminants should utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state, and local agencies...." (§ 39650(d)). In evaluating the health effects associated with proposed TACs, "the office shall consider all available scientific data, including, but not limited to, relevant data provided by ... academic researchers...." (§ 39660(6)).

[40] "The CTS cohort was established from respondents to a 1995 mailing to all 329,000 active and retired female enrollees in the California State Teachers Retirement System (CaISTRS)." Reynolds, p. 30. 116,544 cohort members were followed from this mailing and 2,005 breast cancer subjects identified. Reynolds, p. 31.

[41] Reynolds, p. 29. Breast cancer is a disease of largely unknown etiology. See ACS website, NCI website, supra notes 13, 15; Millikan 1998, p. 377. Thus, it is not surprising persons in different geographic areas have different risks of developing breast cancer.

[42] Reynolds, p. 34.

[43] Reynolds, p. 31, Table 2.

which constitute a substantial portion of the data from the "new studies" reviewed by Cal/EPA since its 1997 Report, do not support an association between breast cancer and ETS exposure.

In summary, little has changed since 1997, when Cal/EPA correctly concluded that there was insufficient evidence linking ETS exposure and breast cancer. If anything, the additional data published since 1997 provide less support for a causal association between ETS and breast cancer than the pre-1997 data. Therefore, Cal/EPA's strained and novel assertion that a causal association exists between ETS and breast cancer is not supported by the scientific data.

Response:

OEHHA thanks this commentator (and several others) for drawing OEHHA's attention to this study, which appeared after preparation of the report's public review draft. OEHHA has included a summary and analysis of this study in the revised report, and also had discussions with the principal author as to the implications and conclusions drawn. It is important to note that the principal conclusion drawn by the authors of this study relates to active smoking, for which they found an association with breast cancer risk. It is incorrect to characterize the data from this study as inconsistent with OEHHA's conclusion, since ascertainment of ETS exposure in the report so far published is limited.

We understand that prospective studies are favored study designs over case-control due to the lessened opportunity for bias. However, all the prospective cohort studies suffered from inadequate exposure characterization. Many relied on a single question regarding exposure to ETS at baseline and did not evaluate exposures in multiple environments (e.g., asked only about spousal smoking). Thus, although the prospective studies did not find statistical associations between breast cancer and ETS exposure, the study design limitations may at least partly explain the lack of association

Comment 10:

Conclusion

The 2003 Draft Report is insufficient to establish ETS as a Toxic Air Contaminant in California. Cal/EPA has not met the specific requirements for establishing a TAC laid out in Sections 39650-39675 of the California Health & Safety Code. Furthermore, the 2003 Draft Report's conclusion that a causal association exists between ETS and breast cancer is not supported by the current record and is inconsistent with additional scientific evidence not cited in the record.

Response:

OEHHA disagrees with the comment's conclusions; see responses to specific comments above.

Comments of Sanford H. Barsky, MD, Professor of Pathology, University of California, Los Angeles (on behalf of R.J. Reynolds Tobacco Company).

Introductory Remarks

I would like to respond to your invitation for written comments concerning your recent report, "Proposed Identification of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant, November 2003. I specifically would like to comment on the section that deals with the risk assessment of ETS and breast cancer.

I am a Professor of Pathology at UCLA, a breast cancer researcher and practicing breast pathologist and I am very much interested in studying the etiologies of human breast cancer and defining the molecular mechanisms behind this very important disease of women.

The current draft of the present report of the Air Resources Board starts out by saying that the evidence linking ETS and breast cancer has considerably strengthened since the 1997 Report was published. The 1997 Report entitled, "Health Effects of Exposure to Environmental Tobacco Smoke", considered the relationship of ETS with breast cancer inconclusive and made the statement that this relationship must be interpreted cautiously (1). The current draft of the present report states, "In comparison to studies reviewed in the previous OEHHA report (Cal/EPA, 1997) current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk.... Overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer....”(2).

Comment 1:

Biomarker Studies.

Let's begin with the biomarker studies. The biomarker studies consist of the demonstration that polycyclic aromatic hydrocarbons (PAH) were found in breast tissue of subjects and higher levels were found in their tumors. The levels of PAH adducts were not observed however to be associated with current active or passive smoking exposure. If one examines all the tissues of the body, the highest levels of PAH-adducts are actually found in heart tissue (3), a tissue that does not give rise to cancer and a tissue that is therefore resistant to the effects of smoking-related carcinogens. So the absolute or relative levels of PAH adducts in of themselves do not constitute a meaningful biomarker. If evidence of molecular damage from the adducts such as mutations could be shown in breast tissue such as the characteristic G-T transversion of PAH or if, phenomenon related to genomic instability, such as loss of heterozygosity (LOH) or microsatellite instability as has been shown to be present in bronchial tissues of smokers (4,5) had been demonstrated in breast tumors of people exposed to ETS that in fact would be evidence of a biomarker. PAH-adducts alone for the reasons cited are not enough. Therefore the weight of biomarker evidence does not support a causal association between ETS and human breast cancer.

Response:

Contrary to the assertion in the comment, several studies have shown that levels of PAH or related aromatic adducts are associated with current and former active or passive smoking exposure. For instance, Firozi et al (2002) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted.

Similarly, Faraglia et al. (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend (P = 0.04) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status (P = 0.03). An increase in adduct levels with passive smoking status alone (never, former, current) was seen but the trend was not statistically significant: a significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking.

The intent of OEHHA's discussions in the document was to point out:

1. *PAHs are found to cause DNA adducts in various tissues.*

2. *Appearance of these adducts correlates with the appearance of tumors at substantial (and therefore easily observable) rates in some tissues.*

3. *Appearance, both of adducts and consequential genetic modifications, correlates with tumor appearance in some tissues.*

4. *Several of these end-points have been demonstrated in breast tissue (in animals or humans) under a variety of circumstances where exposure to PAHs occurred, either as a consequence of exposure to ETS or from some other source. The original report cites various authorities (Li et al. 1999; Perera et al., 1995; Conway et al., 2002; Santella et al., 2000; Rundle et al., 2000; Li et al., 2002). In addition, the finding by Gammon et al. (2002) of an association between PAH adducts, in mononuclear cells from blood samples, and breast cancer should be considered.*

Given these consistent observations, it is reasonable to describe biomarker evidence as supportive of a causal association between ETS and human breast cancer. Neither OEHHA, nor laboratory research scientists active in this field, have sought to establish that there is a quantitative relationship between the different measures of exposure and effect across different tissues, nor would such a relationship be expected given the different metabolic capabilities, susceptibility to mutation and tumorigenesis, and DNA repair capacities of the many different tissues in the body. Breast tissue is clearly a tissue susceptible to cancer; heart tissue is clearly

not. Thus, the argument that the absence of heart cancer in the presence of measurable DNA adducts in heart tissue implies no connection between DNA adducts and cancer in general is invalid. OEHHA is not asserting that the biomarker evidence is sufficient in isolation to establish the causal association between ETS and human breast cancer, but rather that it contributes substantially to the overall weight of evidence in favor of such a conclusion (which is based primarily on epidemiological findings).

Comment 2:

Animal models of breast cancer

Animal models purporting an association of ETS and breast cancer are also lacking. Most animal models of breast cancer are mouse models and are related to either the mouse mammary tumor virus (MMTV) or the genetically engineered mouse (GEM) where certain oncogenes such as myc and neu are overexpressed (6). There are only a few models of PAH induced mammary tumors, the most common example of which is dimethylbenzanthracene (DMBA). However carcinogen-induced mammary tumors including DMBA are not metastatic (6). Hence the scarcity and overall relevance of these murine models to ETS and human breast cancer is questionable. Certainly the weight of the evidence provided by these animal studies is not sufficient to show a causal association between ETS in breast cancer.

Response:

The study cited in the comment is the title (but not session titles or abstract numbers) of a recent symposium at which only a small part of the overall issue of animal models of mammary cancer was addressed. In particular, although some mouse strains (including many C3H and DBA mice) obtain their sensitivity to mammary carcinogens on a latent infection by a mouse mammary tumor virus (MuMTV), other strains, including the B6C3F1 hybrid used as the standard test strain by NTP, do not show the characteristic histological signs of MuMTV infection (Seely and Boorman, 1999). Many chemically induced tumors are classified histologically as carcinomas, and invasion and metastasis are observed (idem). The statement on the "common example … dimethylbenzanthracene (DMBA) … relevance of these <u>murine</u> models is questionable" (emphasis added) appears not to give sufficient consideration to the fact that the usual mammary tumor model with 7,12-DMBA uses the female Sprague-Dawley rat, not the mouse. Contrary to the implication in the comment, the tumors formed in this model are considered to include carcinomas, which by definition are metastatic. Although investigators have shown the involvement of tumor viruses in some models of mammary carcinogenesis in both the rat and the mouse, this is not universal. The comment also appears to discount the possibility that chemical/virus interactions could be relevant to human disease. This is unjustified, since our considerable ignorance in this area is relieved only by a few examples in which such interactions are known to be important (e.g. aflatoxin and Hepatitis B virus which interact in humans to produce liver cancer). With regard to the relevance of animal models to human disease, Thompson and Singh (2000) state:

> "The sequential steps most commonly described in the natural history of breast cancer are: ductal hyperplasia, atypical ductal hyperplasia, carcinoma in situ, and invasive

carcinoma. Evidence will be presented that the development of mammary carcinoma in the rat has a similar natural history."

Evidence of DNA adduct formation, p53 oncogene activation and similar parallel findings in rodent models and in exposed humans was documented in the OEHHA report.

Comment 3:

Past epidemiological studies really have provided the weight of the evidence suggesting a causal association between ETS and human breast cancer but the current draft of the present report either ignores mentioning or does not give the appropriate weight to recent studies which refute this association. Before I cite and discuss these recent studies, I would like to point out some of the shortcomings of many of the previous studies which the current draft cites.

Firstly, it is important to emphasize that human breast cancer is a heterogeneous disease consisting of both life-threatening variants, breast-threatening variants and innocuous variants which are incidental findings. Obviously the first of these disease types is of more concern to the general public than the last of these types. The vast majority of the epidemiological studies cited in the current draft lumps all of breast cancer together. The few studies which look at breast cancer mortality (the first of these disease types) find no association with ETS.

Response:

Breast cancer types may be divided in regards to their histologic type, encapsulation vs metastatic, receptor presence, etc. Other characteristics such as age at discovery have prognostic value. The assertion above that there is a distinction between breast-threatening and life threatening breast cancer as a distinct disease type is inaccurate. While studies appropriately lump various of these issues together for analysis, the studies that review incident data are, in general, pathologically defined breast cancer that is at least potentially life threatening. Breast cancer diagnosis is of great importance to both the individuals that receive that diagnosis and to society in general and the financial cost alone makes this disease highly important to the general public. Unfortunately, there is indeed significant mortality among the cases diagnosed as part of the incident breast cancer studies. While there are clearly differences in the aggressivity of breast cancers (with higher aggressivity associated with those more common in premenopausal cancers for which a stronger association with ETS exposure is evident), the commentator presents no evidence that supports the conclusion that there is a distinction, based on disease causation, between fatal and non-fatal breast cancer as defined in epidemiologic studies.

We are unaware of any accepted diagnostic staging scheme that considers any breast cancer whether found incidentally or upon biopsy completely innocuous. The comment probably refers to DCIS or ductal carcinoma in situ, although that is not specified in the comment. This is a cancer that is confined to the milk ducts and not yet invasive. However, DCIS can and does become invasive in some patients with substantial morbidity and mortality. Furthermore, the comment indicates that "breast-threatening variants" of cancer are not concerning to the public. The treatment of so-called "breast-threatening" breast cancer can involve considerable

morbidity, including mastectomy, and depending on a number of prognostic indicators, chemotherapy and radiation therapy which often follow even when there is no evidence of metastasis. The psychological consequences of mastectomy in and of themselves can be costly in terms of quality-of-life issues for some women. Thus, there is real reason to take issue with the comment's classification of "breast-threatening" variants as not concerning to the public. And finally, death from breast cancer can and does occur even with very favorable prognostic indicators, and even in those originally diagnosed with DCIS. Thus, the comment's contention that some breast cancers are not of concern is invalid.

Also, in this comment it is implied that from an epidemiologic perspective the studies of mortality are actually the most valid and preferred study design. This is not the case. Cancer mortality studies have recognized limitations, particularly those limited to case ascertainment via death certificate. They generally lack information on stage of diagnosis, duration of illness, treatment or other access related issues that influence cancer survival, particularly in cases diagnosed or reoccurring in periods prior to death (and therefore not likely to be listed as a primary or secondary cause of death). The relationship between disease and exposure, particularly in a chronic disease with good survival (at least at early diagnosis), diminishes over time, and potentially is underestimated in the population under study if surveillance is based on death alone.

Comment 4:

Secondly, it is important to emphasize that the data demonstrating a relationship between ETS and human breast cancer must do so in a biologically plausible manner. If there indeed is an association between ETS and human breast cancer, there must be an association between mainstream smoking and breast cancer and the latter association must be stronger. That is so because the carcinogenic exposure is greater with mainstream smoke. Yet none of the epidemiological studies that the current draft cites show a greater association with mainstream smoking (7-11). An argument advanced to reconcile this disparity is that the control group may have consisted, in part, of people exposed to ETS and thus had a higher rate of breast cancer than would have been expected (2). Differences in breast cancer incidence between this control group and the smoking group would have therefore been minimized. However even this argument would fail to explain why the rate of breast cancer was not higher in the smoking group. The smoking group would consist of subjects exposed to mainstream smoke and hence to the maximal levels of carcinogens. The control group even if it was composed of never smokers and subjects exposed to ETS would still have an overall reduced level of carcinogen exposure and therefore a reduced incidence of breast cancer compared to the mainstream smoking group. But that was not what was observed. Smokers did not have a higher incidence of breast cancer than ETS exposed subjects.

Thirdly, none of the epidemiological studies mentioned in the current draft propose a credible biological mechanism to explain the observations of the study on the relationship of ETS to breast cancer. For example, there is no demonstration that people exposed to ETS have a higher level of cotinine or a higher level of DNA adducts or more mutations in their breast tissue than controls.

Response:

The comment indicates that breast cancer could not possibly be caused by ETS if it is not caused by active smoking. The basis for this contention is that active smokers have higher exposures to carcinogens in cigarette smoke than passive smokers. This would only be true if the concentrations and physical state of all tobacco smoke carcinogens are the same in mainstream and sidestream smoke. This is not the case – some carcinogens occur at significantly higher concentrations in side stream smoke due to the different combustion conditions that generate sidestream versus mainstream smoke. In addition, the contention that if active smokers do not have higher rates of breast cancer than passive smokers, ETS could not be a cause of breast cancer in passive smokers also ignores the anti-estrogenic activity of active smoking. Since many breast tumors are estrogen-receptor positive and are dependent upon the presence of estrogen for growth, then anti-estrogenic characteristic of active smoking would actually mitigate effects of carcinogens to some extent. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship (typically, faute de mieux), in this case this assumption is neither necessary, nor supported by the data.

The comment also indicates that the data available on active smoking and breast cancer do not suggest an association. We do not think that is entirely accurate. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of spousal smoking habit as a sole, dichotomous measure of ETS exposure seems inadequate since it largely fails to capture the extent of exposure during the period of greatest sensitivity. There are a number of studies now which note positive associations between active smoking and breast cancer, the recent study (noted by the commentator below) by Reynolds et al. (2004a) being an example. This is a prospective cohort study that has been published since the original draft of this document. In this study of California teachers smoking is significantly associated with development of breast cancer and significant trends are noted with increasing duration and intensity of exposure. Details of this study have been added to the revised document.

The comment also minimizes the effect of exposure misclassification on the studies of passive smoking and breast cancer. We do not agree that this effect is minimal. It is difficult to ascertain exposure to ETS over the long-term past. Most studies do a relatively limited assessment of exposure by asking about either spousal exposure or workplace exposure. However, the studies that did a better job of ascertaining exposure in both and had referent groups that had very minimal exposure show statistical correlations between long-term passive smoke exposure and breast cancer.

Finally, we address the last argument in this comment that " there is no demonstration that people exposed to ETS have a higher level of cotinine or a higher level of DNA adducts or more mutations in their breast tissue than controls". *This is in fact incorrect As discussed in Part A, a*

large number of studies have demonstrated that ETS exposure is measurable via cotinine levels in the blood (see for example Pirkle et al., 1996) In addition, studies have shown elevated PAH DNA adducts in breast tissue of breast cancer patients relative to controls (Rundle et al., 2000), and higher levels of polycyclic aromatic and 4-aminobiphenyl DNA adducts in breast tissue have been observed in smokers relative to nonsmokers (Li et al., 1996; Firozi et al., 2002; Faraglia et al., 2003; see discussion Section 7.4.1.7 Part B).

Comment 5:

Fourthly, the present draft cites many studies with very small numbers of patients (8,12). When dealing with relative risks or odds ratios in the 1.x range, large numbers of subjects are essential for conclusions of statistical significance.

Fifthly, the present draft cites studies which are mainly retrospective and not prospective in nature (10,11,12). Retrospective studies are inherently much weaker than prospective studies. Only a single prospective study (13) is cited by the present draft. This study by Jee et al. showed an increased incidence of breast cancer in spouses exposed to ETS from their husbands' smoking but whether this association rose to statistical significance can be raised.

Response:

The RR for wives of current smokers for greater than 30 years in Jee et al. was 1.7 (95% CI 1.0-2.8). The number of breast cancer cases (n=138) in this study limits the power to detect an association and contributes to the relatively large confidence intervals noted. While study sizes vary amongst the studies reviewed, many had sufficient size to identify relative risks of statistical significance and did so. As well, the OEHHA combined studies, using standard methods, in the summary section. Whether analyzing the studies as a whole or the subset of studies with better measures of exposure OEHHA identified statistically significant associations between ETS exposure and breast cancer. Measures were robust to inclusion or exclusion of any individual studies.

Although prospective cohort studies in general have the potential to be preferable for examination of risk, all of the ETS/breast cancer prospective cohort studies suffer from incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Hertz-Picciotto (1998). A fundamental requirement for study validity is a level of accurancy in exposure ascertainment.In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontam et al., a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements.

The comment that only a single prospective study is presented is not correct. In the original draft four ETS/breast cancer cohort studies are reviewed (Egan, 2002; Jee, 1999; Wartenberg, 200; Nishino, 2001). The discussion of each includes strengths and weaknesses. To these Reynolds et al.(2004a) has been added in the revised document.

Comment 6:

Sixthly, some studies cited in the present draft, e.g. Lash et al. (11), published in 1999 and showing an association between ETS and breast cancer were refuted in subsequent studies by the same authors, eg. Lash et al. (14) in 2002.

Seventhly, the studies linking genetic polymorphisms with breast cancer risk and ETS are inconclusive or show no association between ETS and breast cancer irrespective of polymorphisms (15,16).

Response:

Both papers by Lash et al. are reviewed and considered in the document. The 2002 paper was published as a "brief communication" and so details of the study results are limited. As would be expected, there is not 100% concordance of study results evaluating risk of breast cancer and ETS. The preponderance of the evidence from these studies does, however, support the conclusions reached in the document.

Much of the recent relevant work looking at genetic polymorphisms and susceptibility to breast cancer has been done with active smoking. While we agree that any genetic susceptibility modifying the relationship between tobacco smoke and breast cancer has yet to be firmly established, the majority of studies now find either statistically non-significant or significant interactions between human genetic characteristics, smoking, and breast cancer incidence. The level of statistical significance is a function of the size of these studies which have been limited by financial and other considerations. Additionally, accounting for the full spectrum of interactions necessary to fully explore possible risk is difficult as there may be interactions between age at exposure, age at first pregnancy, intensity and duration of exposure, genetic phenotype, etc. A meta-analysis of the various studies is not feasible since there are few studies which have measured outcomes for the same variables. Below is a chart of recent studies exploring genetic polymorphisms and susceptibility to breast cancer among active smokers which we have added to the active smoking section of the document. As noted in the chart, there are some studies which indicate strong effects of metabolic enzyme profiles, although others may not. Looking at a single enzyme does not give the complete picture because there are many different carcinogens in tobacco smoke metabolized by several different enzymes (both Phase I and Phase II). Thus the resulting net effect for a given individual depends on the entirety of the metabolic enzyme profile as far as dose of ultimate carcinogen is concerned. In addition, Couch et al. (2001) found that those smokers with high familial rates of breast and ovarian cancer have high elevated risk of breast cancer compared to nonsmokers. The point we are making is that genetics plays a role in chemical carcinogenesis and there appears to be susceptible subpopulations for carcinogenicity of tobacco smoke.

Gene Polymorphisms and Genetic Susceptibility to Breast Cancer Among Active Smokers

Study	Polymorphism	Target group	Comparison group	OR (95% CI)
Millikan		**Quit smoke ≤ 3 yr**	Never smoker with and	
et al., 1998	NAT2[1] fast	Postmenopausal	without ETS exposure	7.4 (1.6; 32.6)
		Premenopausal	"	1.5 (0.6; 4.0)
	NAT2 slow	Postmenopausal	"	2.8 (0.4; 8.0)
		Premenopausal	"	1.9 (0.5; 7.9)
		Current smokers		
	NAT2[1] fast	Postmenopausal	"	1.4 (0.7; 2.8)
		Premenopausal	"	1.1 (0.5; 2.3)
	NAT2 slow	Postmenopausal	"	1.1 (0.6; 2.2)
		Premenopausal	"	0.8 (0.4; 1.6)
Morabia	NAT2 fast	Postmenopausal	Never-smoker, no ETS	8.2 (1.4; 46.0)
et al., 2000	NAT2 slow	"	ETS only	2.5 (1.0; 6.2)
	Fast & slow	Premenopausal	Never-smoker, no ETS	2.9 (1.1; 7.5)
Delfino	NAT2	Postmenopausal	Low risk controls	1.29 (0.74 ; 2.27)
et al., 2000		Premenopausal		1.15 (0.49 ; 2.79)
		All ages		1.25 (0.27; 5.82)
Krajinovic	NAT2 fast	BC[2] smokers	BC nonsmokers	2.6 (1.1; 6.3)
et al., 2001		(pre-& post)		
Chang-	NAT2 fast	Pre- and post-	Never-smoker, no ETS	1.22 (0.59; 2.54)
Claude	NAT2 slow	menopausal	"	1.67 (0.67; 2.89)
et al., 2002				
Zheng		Smoke start <18		
et al., 2002	GSTT1[3] null	Postmenopausal	Never-smokers	2.9 (1.0; 8.8)
	GSTT1 positive			1.1 (0.6; 1.9)
	GSTT1 null	Pre- and post-	Never-smokers	1.7 (0.8; 3.7)
	GSTT1 positive	Menopausal		1.0 (0.7; 1.6)
		Current smokers		
	GSTT1[3] null	Postmenopausal	Never-smokers	2.3 (0.6; 8.9)
	GSTT1 positive			1.1 (0.6; 2.1)
	GSTT1 null	Pre- and post-	Never-smokers	1.1 (0.4; 2.7)
	GSTT1 positive	Menopausal		1.1 (0.6; 1.9)
Saintot	Val CYP1B1[4]	Pre- and post-	Leu/Leu nonexposed	2.32 (1.00; 5.38)
et al., 2003	His SULT1A1[5]	menopausal	Arg/Arg nonexposed	2.55 (1.21; 5.36)
	Met COMT[6]		Val/Val nonexposed	1.42 (0.65; 3.13)
Couch	High familial	1st degree relative	Never-smokers	1.8 (1.2; 2.7)
et al., 2001	BC risk	2nd degree	"	1.1 (0.8; 1.5)
		Married in	"	1.2 (0.9; 1.6)
	Highest risk (5+	Sisters and daughters		
	family members	SMR	"	5.8 (1.4-23.9)
	affected)[7]			2.3 (0.9-6.0)

[1]NAT2 = N-acetyltransferase; [2]BC = breast cancer; [3]GSTT1 = Glutathione S transferase T1 [4]CYP1B1 = Cytochrome P-450 1B1; [5]SULT1A1 = Phenol-sulphotransferase 1A1; [6]Catechol-O-methyltransferase; [7]Highest risk families were defined two ways: those with five or more members with either ovarian of breast cancer or those with two or more observed cancers than expected. From the latter definition was derived the number based on the SMR.

Comment 7:

Finally and most importantly the present draft fails to cite or properly acknowledge the importance of recently emerging powerful and compelling prospective studies published since 2000 all of which have showed no association between ETS and breast cancer (17-20). These prospective studies have the power of large number of subjects enrolled and have been published in peer reviewed journals of the highest impact factors. In the first study, the Reynolds study (2004) (17), which was just recently published, it was found that 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. Furthermore, breast cancer risks among never smokers reporting household passive smoking exposure were not greater than those among never smokers. Their study provided evidence that active smoking but not passive smoking exposure may play a role in breast cancer etiology.

Response:

We agree that the evidence linking active smoking with breast cancer is strengthened by Reynolds et al. (2004a). The study as published has the same limitations of the other prospective studies. That is, the exposure assessment for ETS is limited to 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 et al., 2004b)

Comment 8:

In the second study, the (Wartenberg study (2000) (18), the authors concluded that, "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". The third study, Nishino et al. (19), and the fourth study, Egan et al. (20) are also both prospective studies showing no relationship between ETS and breast cancer.

Because of all these cited reasons, I am concerned that the conclusion of the present draft concerning the relationship between ETS and breast cancer simply is not supported by the data and that the most recent and most powerful studies have not strengthened the association between ETS and breast cancer but actually weakened it. It is important in considering the totality of evidence not simply to add up the studies for and against an observation but to rank order the studies. All studies in science are not created or conducted equally ! For example studies with large numbers, of subjects, all other things being equal, are superior to studies with a small number of subjects. Prospective studies, all other things being equal, are superior to retrospective studies. Studies published in highly regarded peer reviewed journals with high impact factors (the average number of times their articles are quoted by other studies), all other things being equal, are superior to studies published in less known journals with low impact factors. Studies which are peer reviewed are superior to studies which are not peer reviewed such as letters to the editor, etc.

Response:

We have indicated clearly that three large prospective studies in the United States (Eganet al., 2002; Wartenberg et al., 2000; Reynolds 2004a [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure, that these studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer; and that in at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. Although these cohort studies in general have the potential to be preferable for examination of risk, all three of these studies suffer from seriously incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Hertz-Picciotto (1998) and was addressed in the earlier draft for the first two studies and in the revised draft for the Reynolds paper. A fundamental requirement for study validity is a level of accurancy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all important measures of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontham et al.(1991;1994), a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements.

Comment 9:

Simply stated, the studies which show no association of ETS with breast cancer are prospective, comprised of large numbers of subjects, recent and published in journals of the highest impact factors (17-20). The studies which show a relationship of ETS with breast cancer are retrospective, comprised of a small number of subjects, older and published in low impact journals (8,10,12) or published not as peer reviewed articles at all but rather as letters to the editor (21,22).

Response:

The above comment is misleading. While we agree that references 17 through 20 are large prospective studies published in peer reviewed journals the implication that the studies finding an association with ETS are old, small, and published in "low impact" journals is not correct. First, the papers reviewed in the draft document were published since the previous volume (1997) so none were "old". We added some further discussion of a few prior studies which had few details in our original volume. As far as the size of the retrospective studies being "small", examples of study enrollment include; Johnson et al. (2000) with over 2,300 incident primary breast cancer cases, Millikan et al. (1998) had 498 cases and 473 controls, Morabia (1996) had 244 cases and 1,032 controls, and Kropp and Chang-Claude (2002) with 197 cases and 459 controls. The journals in which these were published include Cancer Causes and Control, Cancer Epidemiology Biomarkers and Prevention, American Journal of Epidemiology (Morabia and Kropp and Chang-Claude). These are highly respected and influential journals. The letters

to the editor are cited for reference only and do not include primary study data except where corrections have been published.

Comment 10:

It is also pertinent to point out to the Air Resources Board that another environmental protection agency, the International Agency for Research on Cancer, whose overall mission is similar to that of the California Environmental Protection Agency and who, in the past, has warned the public about the risks of smoking and the dangers of ETS issued the following report in 2002: "Concerns that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking is unjustified by the evidence" (23). Their report further goes on to state: "The collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent. Although 4 of the 10 case control studies found statistically significant increased risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal association between involuntary exposure to tobacco smoke and breast cancer in never smokers. The lack of a positive dose response also argues against a causal interpretation of the findings. Finally the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking."

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 and metadata than those used by IARC.

Comment 11:

Certainly both mainstream smoking and exposure to ETS are not good things for our society to have to deal with and it would be best if these practices could be eliminated. But it is important to accurately evaluate which diseases are and which diseases are not associated with either exposure.

One may ask what is the danger of overstating a potential risk factor in the etiology of any disease. The danger is that it will detract from finding the real culprit. In the case of breast cancer, we really do not know what the cause of the disease is and we need to find out. We need also to identify the major risk factors (both environmental and genetic) to explain sporadic breast cancer, by far the most common type of breast cancer.

Response:

We agree that the conclusion in relation to breast cancer and smoking is extremely important. We consider that the "credibility of the review process" is equally jeopardized by a premature decision in favor of causality and by a failure to respond to new and important findings and analyses that support that conclusion. We have received a number of comments about this conclusion, some supportive and some not. Having carefully reviewed the comments by Dr. Barsky and others we conclude that the existing evidence indicates that the association between ETS exposure and increased incidence of breast cancer may reasonably be considered causal.

Comment 12:

As presently stated, the current working draft of the Air Resources Board claims that overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer. I fear that this current draft has not given enough weight to the newer emerging prospective studies that have been published in outstanding peer review journals of high impact factors that show no association of ETS with breast cancer and has ignored the recent 2002 report of the International Agency for Research on Cancer that also concludes that there is no such association. These studies should be acknowledged and the report's conclusions about the association of ETS and human breast cancer should at least be modified in the face of this new emerging data.

I would hope that the arguments advanced in this letter would cause the Air Resources Board to at least rethink its position on this matter.

Response:

OEHHA disagrees with the conclusions expressed in this comment, as noted in the earlier detailed responses.

Concluding remarks:

I wish to disclose to the Air Resources Board that I was contacted by R.J Reynolds and asked to review the current draft of the report of Chapter 7, conduct a review of the medical and scientific literature on breast cancer and ETS and prepare my written comments. I was compensated for the time spent on these endeavors.

References cited in comments

1. California EnvironmentalProtection Agency, Office of Environmental Health Hazard Assessment, Health Effects of Exposure to Environmental Tobacco Smoke, Final Report, September, 1997.

2. California Environmental Protection Agency, Air Resources Board, Office of Environmental Health Hazard Assessment, Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant [Draft], December 2003.

3. Randerath E, Miller RH, Mittai D, Avitts TA, Dunsford HA, Randerath K. Covalent DNA damage in tissues of cigarette smokers as determined by 32P-postlabeling assay. J Natl Cancer Inst 81: 341-347, 1989.

4. Wistuba 11, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, Samet JM, Srivastava S, Minna JD, Gazdar AF. Molecular damage in the bronchial epithelium of current and former smokers. J Natl Cancer Inst 89: 1366-1373, 1997.

5. Mao L, Lee JS, Kurie JM, Fan YH, Lippman SM, Lee JJ, Ro JY, Broxson A, Yu R, Morice RC, Kemp BL, Khuri FR, Walsh GL, Hittelman WN, Hong WK. Clonal genetic alterations in the lungs of current and former smokers. J Natl Cancer Inst 89: 857-862, 1997. 6. Advances in human breast cancer research: Preclinical models. The 24th Congress of the International Association for Breast Cancer Research. Sacramento, CA 2003.

7. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. Am J Epidemiol 156: 616-626, 2002.

8. Morabia A, Bernstein M, Heritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. Am J Epidemiol 143: 918-928, 1996.

9. Smith SJ, Deacon JM, Chilvers CED. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. Br J Cancer 70: 112-119, 1994.

10. Johnson KC, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994-1997. Cancer Causes and Control 11: 211-221, 2000.

11. Lash TL, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. Am J Epidemiol 149: 5-12, 1999. 12. Sandler DR, Everson RB Wilcox AJ. Passive smoking in adulthood and cancer risk. Am J Epidemiol 121: 37-48, 1985.

13. Jee SH, Ohrr H, Kim HS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. International J Epidemio128: 824-828, 1999.

14. Lash TL, Aschengrau A. A null association between active or passive cigarette smoking and breast cancer risk. Breast Cancer Res Treat 75: 181-184, 2002.

15. Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao SY, Gim JSY, Ma HL, Butler J, Anton-Culver H. Breast cancer passive and active Cigarette smoking and N-acetyltransferase 2 genotype. Pharmacogenetics 10: 461-469, 2000.

16. Millikan RC, Pittman GS, Newman B, Tse CKJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA. Cigarette smoking, Nacetyltransferase 1 and 2 and breast cancer risk. Cancer Epidemiology Biomarkers and Prevention 7: 371-378, 1998.

17. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A. Active smoking household

passive smoking and breast cancer: Evidence from the California Teachers study. J Natl Cancer Inst 96: 29-37, 2004

18. Wartenberg D, Calle EE, Thun MJ, Heath CW, Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. J Natl Cancer Inst 92: 1666-1673, 2000.

19. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes and Control 12: 797-802, 2001.

20. Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA. Active and passive smoking in breast cancer: Prospective results from the nurses' health study. Epidemiology 13: 138-145, 2002.

21. Wells AJ. Breast cancer, cigarette smoking and passive smoking. Am J Epidemiol133: 208-210, 1991.

22. Wells AJ. Breast cancer, cigarette smoking and passive smoking. Am J Epidemiol 147: 991-992, 1998.

23. Press Release, IARC Monographs Programme declares secondhand smoke carcinogenic to humans. International Agency for Research on Cancer, 2002.

References cited in Responses

Chang-Claude J, Kropp S, Jager B, Bartsch H, Risch A (2002). Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 11(8):698-704.

Conway K, Edmiston SN, Cui L, Drouin SS, Pang J, He M, Tse CK, Geradts J, Dressler L, Liu ET, Millikan R, Newman B (2002). Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. Cancer Res 62(7):1987-95.

Couch FJ, Cerhan JR, Vierkant RA, Grabrick DM, Therneau TM, Pankratz VS, Hartmann LC, Olson JE, Vachon C M, Sellers TA (2001). Cigarette smoking increases risk for breast cancer in high-risk breast cancer families. Cancer Epidemiol Biomarkers Prev. 10(4):327-32.

Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao S, Gim JS-y, Ma HL, Butler J, Anton-Culver H (2000). Breast cancer, passive and active cigarette smoking and N-acetyltransferase 2 genotype. Pharmacogenetics 10(5):461-9.

Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA (2002). Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. Epidemiology 13(2):138-45.

Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003). Evaluation of 4-aminobiphenyl-

DNA adducts in human breast cancer: the influence of tobacco smoke. Carcinogenesis 24(4):719-25.

Firozi PF, Bondy ML, Sahin AA, Chang P, Lukmanji F, Singletary ES, Hassan MM, Li D (2002). Aromatic DNA adducts and polymorphisms of CYP1A1, NAT2, and GSTM1 in breast cancer. Carcinogenesis 23(2):301-6.

Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, *et al.* (1994). Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA 271(22):1752-9.

Fontham ET, Correa P, Wu-Williams A, Reynolds P, Greenberg RS, Buffler PA, Chen VW, Boyd P, Alterman T, Austin DF (1991). Lung cancer in nonsmoking women: a multicenter case-control study. Cancer Epidemiol Biomarkers Prev 1(1):35-43.

Gammon MD, Santella RM, Neugut AI, Eng SM, Teitelbaum SL, Paykin A, Levin B, Terry MB, Young TL, Wang LW, Wang Q, Britton JA, Wolff MS, Stellman SD, Hatch M, Kabat GC, Senie R, Garbowski G, Maffeo C, Montalvan P, Berkowitz G, Kemeny M, Citron M, Schnabel F, Schuss A, Hajdu S, Vinceguerra V (2002). Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. Cancer Epidemiol Biomarkers Prev. 11(8):677-85.

Jee SH, Ohrr H, Kim IS (1999). Effects of husbands' smoking on the incidence of lung cancer in Korean women. Intl J Epidemiol 28(5):824-8.

Krajinovic M, Ghadirian P, Richer C, Sinnett H, Gandini S, Perret C, Lacroix A, Labuda D, Sinnett D (2001). Genetic susceptibility to breast cancer in French-Canadians: role of carcinogen-metabolizing enzymes and gene-environment interactions. Intl J Cancer 92(2):220-25.

Kropp S, Chang-Claude J (2002). Active and passive smoking and risk of breast cancer by age 50 years among German women. Am J Epidemiol 156(7):616-26.

Li D, Wang M, Dhingra K, Hittelman WN (1996). Aromatic DNA adducts in adjacent tissues of breast cancer patients, clues to breast cancer etiology. Cancer Res 56:287-293.

Li D, Wang M, Firozi PF, Chang P, Zhang W, Baer-Dubowska W, Moorthy B, Vulimiri SV, Goth-Goldstein R, Weyand EH, DiGiovanni J (2002). Characterization of a major aromatic DNA adduct detected in human breast tissues. Environ Mol Mutagen 39(2-3):193-200.

Li JS, Peat JK, Xuan W, Berry G (1999). Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol 27(1):5-13.

Millikan RC, Pittman GS, Newman B, Tse CJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA (1998). Cigarette smoking, N-acetyltransferase 1 and 2, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 7(5):371-78.

Morabia A, Bernstein M, Heritier S, Khatchatrian N (1996). Relation of breast cancer with passive and active exposure to tobacco smoke. Am J Epidemiol 143(9):918-28.

Morabia A, Bernstein MS, Bouchardy I, Morris MA (2000). Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. Am J Epidemiol 152(3):226-32.

Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S (2001). Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Cont 12(9):797-802. (Chapter 7)

Perera FP, Estabrook A, Hewer A, Channing K, Rundle A, Mooney LA, Whyatt R, Phillips DH (1995). Carcinogen-DNA adducts in human breast tissue. Cancer Epidemiol Biomarkers Prev 4(3):233-8.

Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR (1996). Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. JAMA 275(16):1233-40.

Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A (2004a). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. J Natl Cancer Inst. 96(1):29-37. Reynolds (2004b).correspondence JNCI 96 (13) 1042-3,

Reynolds P, Hurley S, Goldberg DE (2004b). Re: Active smoking, household passive smoking, and breast cancer: Evidence from the California Teachers Study – Response J Natl Cancer Inst. 96 (13) 1042-43.

Rundle A, Tang D, Hibshoosh H, Estabrook A, Schnabel F, Cao W, Grumet S, Perera FP (2000). The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. Carcinogenesis 21(7):1281-9.

Saintot M, Malaveille C, Hautefeuille A, Gerber M (2003). Interactions between genetic polymorphism of cytochrome P450-1B1, sulfotransferase 1A1, catechol-o-methyltransferase and tobacco exposure in breast cancer risk. Int J Cancer 107(4):652-7.

Santella RM, Gammon MD, Zhang YJ, Motykiewicz G, Young TL, Hayes SC, Terry MB, Schoenberg JB, Brinton LA, Bose S, Teitelbaum SL, Hibshoosh H (2000). Immunohistochemical analysis of polycyclic aromatic hydrocarbon-DNA adducts in breast tumor tissue. Cancer Lett 154(2):143-9.

Seely JC and Boorman GA 1999. Chapter 23 in Pathology of the Mouse, Maronpot R, Editor, Cache River Press, Vienna, IL

Thompson HJ, Singh M (2000). Rat models of premalignant breast disease. J Mammary Gland Biol Neoplasia. 5(4):409-20.

Wartenberg D, Calle EE, Thun MJ, Heath CW, Lally C, Woodruff T (2000). Passive smoking exposure and female breast cancer mortality. J Natl Cancer Inst 92(20):1666-73.

Zheng T, Holford TR, Zahm SH, Owens, PH, Boyle P, Zhang Y, Wise JP Sr., Stephenson LP, Ali-Osman F (2002). Cigarette smoking, glutathione-s-transferase M1 and t1 genetic polymorphisms, and breast cancer risk (United States). Cancer Causes Control 13(7):637-45.

Comments of Mr. Jay R. Schrand.

Comment 1:

Part B: Health Effects
New developments since the last evaluation in 1997:

Comment:

Missing from all studies on the purported harmful effects of tobacco use on morbidity and mortality, is an analysis of the confounding influence of exposure to Adverse Childhood Experiences (ACE's) and of the stress of the Anti-tobacco program itself.

Background: In this series of studies, ACE's, being exposed to child abuse or household dysfunction had a graded influence on a host of risky behaviors including tobacco use, alcohol and drug abuse, paternity and teen pregnancy, depression, attempted suicide and eating disorders. ACE's also have an independent, graded effect on mortality. Feletti acknowledges that Nicotine may have beneficial psychoactive effects regulating affect, and mood, consequences of depression. Nicotine is well known for reducing stress and increasing attention span. Does tobacco use really cause stress related heart disease? Or is tobacco use simply a marker for stress? Unfortunately, the article, does not present the intercorrelations between ACE's, tobacco use and mortality. This would be a difficult model, but is still significant by its absence. We would not expect that the stress of exposure to ACE's to effect (non-stress related) cancers of the respiratory system. However, stress in implicated in <u>every</u> other illness attributed to tobacco use.

Response:

Most epidemiological studies of the adverse health effects of ETS adjust the studies for confounders related to socioeconomic status or SES. Since stress and resulting behavioral consequences is strongly influenced by poverty, then appropriate confounder adjustment for SES is likely to reduce any effects of what the comment refers to as ACES, assuming these originate from poverty. Also, the comment ignores the fact that there are a number of toxic constituents of tobacco smoke that provide a biological plausibility for adverse health effects noted including particulate matter, CO, aldehydes, a host of carcinogens, and so on.

Comment 2:

The confounding influence of ACE's as it applies to maternal smoking and Fetal Growth and Preterm Delivery (FG&PtD), including BW, LBW, IUGR, SGA.

Several studies have included some of the measures of stress: adverse adult life experiences, trait anxiety, current stress, and domestic violence during pregnancy. However, none have measured the entire range to include ACE's.

A case control study of partner abuse and LBW (Campbell 1999) found that < 15 pound weight gain, spousal abuse and smoking during pregnancy was associated with LBW in full term infants, but only < 15 pound weight gain was related in preterm infants. Smoking was not included in the final adjusted model(assuming that it did not influence the final model). Stress (Daily Hassles Scale) was associated with abuse, but not LBW. The author suggests that "Abuse may be one of a cluster of difficult life experiences that affect birth weight"

One interesting (n=1861) Urban prospective study (Orr 1996) of psychosocial stressors and LBW found that African Americans have a higher rate of LBW and correlation with Moderate/High Stressors and hypertension, whereas the Caucasian population has a lower rate of LBW which is more highly correlated with hypertension, low pre-pregnancy weight, smoking and drug use.

The prevalence of high levels of stressors and established risks (including smoking) in this study was similar in both races. Yet, the risk (odds ratio) for smoking is 6.89 for Caucasians and 1.57 in African Americans. Smoking is a greater risk factor for LBW for Caucasians than it is for African Americans? How can this possibly be?

Table 1

	Caucasian n= 428 LBW= 32		**African-American** n=1433 LBW=156	
	P-value	Odds Ratio	P-value	Odds Ratio
Moderate/High Stressors	.10	.48	.03	1.52
Low Pre-pregnancy Weight	.17	2.29	.005	2.13
Hypertension	.002	15.11	.02	2.93
Smoking	.002	6.89	.03	1.57
Drug Use	.05	2.95	.18	1.48

Table 2

	Caucasian	**African-American**
LBW rate (1990/1995)	5.7/6.22	13.25/13.13
Smoking rate (1990/1995)	23.5/23.4%	20.8/23.5
Decrease in Smoking rate (1990/1995)	.4%	- 13%
Smoking/preg rate (1990/1995)	19.4/15.0%	15.9/10.6%
Decrease in Smoking/preg rate (1990/1995)	22.6%	33.3%

Health, United States, 2003 Trend Tables (tables 10,12,59)
http://www.cdc.gov/nchs/products/pubs/pubd/hus/03hustop.htm

From 1990 to 1995 smoking rates in the US for African American females increased, pregnant African American females decreased 33% as compared to 22.6% for Caucasians(Table 2). One would have to assume that pregnant females in the US were especially targeted with anti-smoking programs, with African American females getting the extra heavy dose. During this time, there was no significant decrease in the rate of LBW(Table 2). Recognizing that those who do quit are the easy ones, with a low Nicotine Tolerance score and associated risks for tobacco related illnesses anyway, one would have to question the utility of the anti-smoking program in the first place.

The author speculates that "a minority group, traditionally suffering exploitation and discrimination, may react differently to stressors than their Caucasian counterparts."

Indeed, this may be because of an increase in genetic susceptibility over several generations. It may also be because of the (cumulative) effect of stressors that were not identified in the Prenatal Social Environment Inventory (PSEI) survey instrument. The author made it a point to include measures of chronic stressors (during the past 12 months) that were unique to African American culture. This apparently lowered their odds ratio for smoking to a paltry 1.57 that, while still "significant", is still highly subject to unknown confounding factors, such as ACE's, partner abuse, and exposure to heavy doses of anti-tobacco messages.

Stress can be mitigated by periods of down time: social support, security, economic prosperity, and sated sleep. For black females, typically raising families alone, this is especially problematic. Societies help too often involves sending critical messages, marginalizing those who appear outside the norm. So, we have an at risk population that has suffered exploitation, and discrimination because they are black and female and now because they smoke. We as a society have come so far, and yet, still such a long distance to go.

Response:

The comment brings up a number of important differences between Caucasians and African-Americans in terms of societal stress factors and stress levels. These important factors may indeed influence birth outcome. However, there are a number of large studies that demonstrate that ETS exposure can influence birth outcome that adjust for SES. Any confounder adjustment will not be perfect, but the association is still present after adjusting for these confounders.

Comment 3:

As it applies to studies of pregnant non-smoking spouses of smokers (ETS):

Refer to Chapter 3. Developmental Toxicity - 1. Perinatal Manifestations

3.2 Fetal Growth and Preterm Delivery

None of the studies of ETS and FG&PtD have included ACE's in the parents. Those who are exposed to ACE's are more likely to smoke. The presence of measures of ETS (Cotinine) in the mother (or child) even though she does not actively smoke may be a marker for exposure to ACE's in the mother or because of assortive mating(discussed below), in the biological father who smokes. Either biological parent may transfer the genetic risk for FG&PtD. The father, because he smokes and is at increased risk for ACE's, may also be at increased risk for spousal abuse during pregnancy, another risk factor for FG&PtD. Paternity is a marker for ACE's also an issue. The same would apply to biological relatives living in the home.

Response:

The point of this comment is not clear. The presence of cotinine is a chemical marker for recent ETS exposure, not for distant exposure.

Comment 4:

As it applies to studies of infants of non-smoking spouses of smokers (ETS):

Refer to Chapter 4. Developmental Toxicity - II. Postnatal Manifestations

4.1 Sudden Infant Death Syndrome (SIDS)

None of the studies of ETS and SIDS have included ACE's in the parents. The same analysis as above applies.

Response:

The studies of SIDS have been well-conducted and do include correction for SES, maternal education and a number of other important risk factors. The comment does not provide a

method to include "ACEs" as a confounder in a meaningful way in an epidemiological study. For example, how would one determine a method to measure "ACEs"?

Comment 5:

Animal Models

Animal are not reliable models of human exposure. In all studies that I am aware of, animals do not select to use tobacco (nicotine). Humans do choose actions to preserve and enhance life.

Tobacco has been in use for 2000 years. Those who smoke are not dying off in their 20's.

Response:

Comment noted. We disagree that animals are not meaningful models of toxicological effects. The statement is contrary to a large body of evidence. The toxicological effects of a large number of substances including nicotine have been elucidated in animal models, and are clearly applicable to humans.

Comment 6:

Biomarkers of Exposure

Is it the Nicotine? Well, as it turns out, there is no Nicotine in ETS. Cotonine, one of the metabolites of Nicotine can be measured as a proxy. Is it Benzene or Vinyl Chloride (Table 7-4D). Both are identified as carcinogens by the IARC. There has not been any identification as to exactly which of the purported harmful constituents causes the specific illnesses or conditions associated with exposure to ETS. In fact, if the particular constituent could be identified, the manufacturing process could be changed to eliminate the harmful constituent.

There is no safe exposure? If you apply this idea to the extreme, it implies that <u>any</u> exposure to ETS is harmful. In other words, a person smoking in Los Angeles could theoretically effect the health of someone in Washington, DC. Of course, this is ludicrous. Unless the specific constituent of tobacco is identified, and the exact amount and time exposure required (not just the risk) to cause cancer, then it would be improper to regulate it as toxic.

Response:

The commenter is misinformed as to the relationship between nicotine and cotinine. As explained in Part A of the document, nicotine does occur in tobacco smoke, whether mainstream, sidestream or environmental. Cotinine is formed by metabolic conversion in the body of a smoker or ETS exposed, and is excreted in the urine: it is not a component of the smoke.

There are clearly a number of chemicals in ETS that are pharmacologically and toxicologically active. It is not necessary to ascertain which chemicals are the most important actors in producing the effects noted in epidemiological studies. It is not clear to date which are the most

important lung carcinogens in tobacco smoke and which interactions among those carcinogens are the most critical, yet it is quite clear from epidemiological studies that cigarette smoking causes lung cancer.

Comment 7:

Assortive Mating

A recent letter (Willensen 2003) commenting on a study (Price 2003) of spousal similarities found that "assortative mating should not be hastily dismissed as a cause for spouse similarities in disease". Part of the risk for cancer is genetic susceptibility. The spouse, through assortment for these factors (including ACE's) is based on similarity at the time dating began, is likely to have an increased risk for these same factors.

Response:

Since the spouse is not genetically related to their mate, the point in this comment regarding genetic susceptibility is not clear. While humans tend to marry within their social strata, and disease rates are related to poverty, it is likely that there are factors in common for diseases that are related to lifestyle, income, and so on. However, since the majority of epidemiological studies account for lifestyle factors primarily by looking at SES (and related correlated factors like education), then confounding by these factors in studies of ETS (or active smoking for that matter) is diminished.

Comment 8:

The social effects of ACE's, stress and the Anti-tobacco program

ACE's and the resultant stress have a cumulative effect, especially on the neuro-hormonal, fight or flight system. Time, social support, and a good nights sleep will help recover from stress. Too much unresolved stress leads to post traumatic stress syndrome and aberrant behavior. An individual from a dysfunctional family with few resources has an uphill battle. This at-risk population has already been exposed to more than their share of dysfunctional authority figures and in extreme cases, actual child abuse. Characteristic of this experience is the use of excessive control, distorted guilt, marginalization, and copious punishment. Survivors of these challenging childhoods are all too often mistaken for easy targets for exploitive behavior.

The current cessation programs rely heavily on the use of distorted blame, social ostracization and punishment in the form of job discrimination and exorbitant taxes. The anti-tobacco program forces a choice between two paths, both with negative consequences. It simply produces conflict and adds ....more stress, to those at greatest risk. This unproductive stress increases illness. No study to date has evaluated the extent of this unintended program effect. This thorough analysis needs to be done, especially in the stress sensitive pregnant women (Relier 2001,Meyers 1977) and those exposed to high levels of trauma and stress in the Military/Veteran (Hourani, 1999) populations. Much more effective cessation methods need to

be offered, long before health care spends money on programs that appear to continue and institutionalize the dysfunctional relationship that many were exposed to in their youth.

Response:

Although OEHHA is not involved in developing smoking cessation programs, the fact remains that smoking is a big physiological stressor. Active smoking causes both lung and heart disease and is associated with a number of cancers. Smoking cessation is probably one of the best things anyone can do for their health.

References in comments:

Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, et al. Adverse Childhood Experiences and Smoking During Adolescence and Adulthood. JAMA. 1999;282:1652-1658

Campbell J, Torres S, Ryan J, King C, Campbell DW, Stallings RY, Fuchs SC. Physical and nonphysical partner abuse and other risk factors for low birth weight among full term and preterm babies: a multiethnic case-control study. Am J Epidemiol. 1999 Oct 1;150(7):714-26.

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998 May;14(4):245-58.

Hourani LL, Yuan H, Bray RM, Vincus AA. Psychosocial correlates of nicotine dependence among men and women in the U.S. naval services. Addict Behav. 1999 Jul-Aug;24(4):521-36.

Myers RE. Production of fetal asphyxia by maternal psychological stress. Pavlov J Biol Sci 1977 Jan-Mar;12(1):51-62.

Orr ST, James SA, Miller CA, Barakat B, Daikoku N, Pupkin M, Engstrom K, Huggins G. Psychosocial stressors and low birthweight in an urban population. Am J Prev Med 1996 Nov;12(6):459-466.

Price RA, Vandenberg SG. Spouse similarity in American and Swedish couples. Behav Genet 1980; 10: 59-71.

Relier JP. Influence of maternal stress on fetal behavior and brain development. Biol Neonate 2001 Apr;79(3-4):168-71.

Shalev E, Eran A, Harpaz-Kerpel S, Zuckerman H. Psychogenic stress in women during fetal monitoring (hormonal profile). Acta Obstet Gynecol Scand 1985;64(5):417-20.

Willemsen G, Vink JM, Boomsma DI. Letter - Assortative mating may explain spouses' risk of same disease BMJ 2003;326:396 (15 February).
http://bmj.bmjjournals.com/cgi/content/full/326/7385/396/a#Fu1

Comments of Linda Stewart

Comment 1:

In 1997, based on a number of uncertain assumptions, questionable epidemiology and ballpark statistics (from 1995) OEHHA concluded that: "the proportion of all low birthweight newborns in California that may be associated with ETS... corresponds to 1,200 to 2,200 in California in 1995..." and to 9,700 to 18,600 in the nation as a whole (in 1995.)

In 2003, OEHHA now estimates 1,577-1,943 cases of ETS associated low birth weight in California and 24,253- 29,590 in the nation.

These new national numbers (which have seemingly increased by up to 14,000) are based on a single sub-set, (adult females of all ages) from the NHANES (Pirkle) survey of 1995 (published in '96) which was actually conducted between 1988 and 1991, and which attempted to quantify the exposure of nonsmokers to secondhand smoke (Footnote 1, p, ES-11)

But let's note that a similar survey, NHANES 1999 ("Second National Report on Human Exposure to Environmental Chemicals") showed a 75% decrease in serum cotinine levels in American nonsmokers, indicating (if anything) that exposure to ETS had considerably declined since the earlier report.

Response:

Smoking prevalence among pregnant women and in the population in general has indeed decreased since 1985. However, between the first (CDC, 2001 pp. 33,34) and second (CDC, 2003, pp. 79,80) National Reports on Human Exposure to Environmental Chemicals, serum cotinine levels have actually risen in parallel with the increase in LBW. In women in the 75th and 90th percentiles, serum cotinine rose 1.49- and 1.85-fold, respectively. Thus a decrease in the median population cotinine level masks increases among women in the upper half of the exposure range. Use of the average cotinine level, reflecting a 75% decrease, is inappropriate because this decrease reflects changes in numbers of persons exposed as well as amount of exposure and does not differentiate between unexposed and exposed. A more appropriate level to use is a level that indicates ETS exposure. That is what was done by OEHHA.

Comment 2:

I therefore find it disturbing that you'd bypass the later study and choose to employ the former, since using the former stats would over-estimate current exposure.

Then too, and just dealing with the national projections, we ought to consider this. (All stats from the CDC.):

UNITED STATES

Year	total % smokers	% pregnant smokers	% LBW of total births
1985	30.2	NA	6.8
1989	[26.8*]	19.5	7.0
1995	24.7	13.9	7.3
1997	24.7	13.2	7.5
2000	23.3	12.2	7.6
2001	22.8	12.0	7.7
2002	[22.5]**	11.4	7.8

* 1989 estimate based on available figures for 1988 (28.1) and 1990 (25.6)
** Average of available figures for 2002.

In other words, while smoking declined 25% and exposure to others' smoke declined 75%, and the number of pregnant smokers declined 40%+ between 1985 and 2002, low birth rates actually rose-- in fact, per the New York Times, to the highest observed levels in the last 30 years. (NY Tlmes, June 26, 2003)

Further, during the period many other suspected risks (teen pregnancy and alcohol consumption by pregnant women) were also in a decline, while preventive measures increased --with record numbers of women getting early pre-natal care. Logically, at least, this should lead to a clear conclusion that the formerly fingered risks, including smoking and ETS, were not as "causative" as was thought. And that productive investigation should begin on another track.

Response:

As mentioned in the response above, smoking prevalence among pregnant women and in the population in general has indeed decreased since 1985. However, between the first (CDC, 2001, pp 33-34) and second (CDC, 2003, pp. 79,80) National Reports on Human Exposure to Environmental Chemicals, serum cotinine levels have actually risen in parallel with the increase in LBW. In women in the 75th and 90th percentiles, serum cotinine rose 1.49- and 1.85-fold, respectively.

Comment 3:

In light of these easily collected statistics, one wonders why OEHHA relied on a single survey of self-reported exposure for women of all ages for 1995 and factored in none of the later relevant clues.

Response:

If the concern is that the updated calculations are inaccurate because they are based on out-of-date data, an alternative calculation of estimated cases for low birth weight due to ETS exposure for the US based on CDC's 2002 National Vital Statistics Report for the year 2000 can be made as follows. In 2000 there were 4,058,814 live births of which 126,241 were multiple, and

3,932,573 were singleton births. Based on the reported numbers of twin (118,916), triplet (6,742), quadruplet (506) and higher order births (77), we estimate that approximately 61,847 women gave multiple births. Thus 3,994,420 women (3,932,573 + 61,847) gave birth in 2000. While there was some variation in active smoking rate with age, the overall smoking rate was 12.2% giving 487,319 smoking, and 3,507,101 nonsmoking mothers. According to the Second National Report on Human Exposure to Environmental Chemicals (CDC, 2003), among nonsmoking women, the serum continine levels for the 75th percentile was 0.179 ng/ml. Thus 25% of nonsmoking women had serum cotinine above this level, indicating exposure to tobacco smoke. Of the nonsmoking mothers, 876,775 (3,507,101 x 0.25) were estimated to be exposed to ETS, which gives an exposure rate of 21.95% (876,775/3,994,420), similar to the 22.7% estimate used above (Pirkle et al., 1996). Thus, use of the 2000 data versus the 1995 data results in similar estimates of exposure and therefore risk. The increased numbers of low birth weight children reflect, in part, population increases.

Comment 4:

Questions arise, too, on the California estimates:

Since 1998, California, in isolation, has virtually ended all exposure to public smoke and boasts of cutting its rates of smoking by incredibly large amounts (about 5%z% below the national average) which would further reduce exposure. Then too, Public Health has so terrified pregnant women on the dangers of ETS, that most women would sooner divorce than let their husbands smoke in the house. Yet the lower range of your estimate has somehow actually climbed (by 377, or 32%)while the upper range has declined by a mere 257. Surely if ETS were a genuine causative factor, your estimate should have declined -- and declined rather drastically-- at both ends of the pole.

So your numbers continue to baffle.

Response:

To clarify a point, in this update we estimated 1,577 excess cases of LBW. The value of 1,943 to which the comment alludes as an upper estimate of LBW is the estimate for pre-term delivery (PTD). The table describing attributable risks was changed during translation into PDF in the Executive Summary and thus in error – the same table in Part B was correct. We apologize for the resulting confusion.

The 1997 OEHHA document used the following equation from the US EPA to calculate the attributable fraction for low birth weight. $a = (1-P_S)(P_E)(R_E-1)/[(1-P_S)(P_E)(R_E-1) + P_S(R_S(P_ER_E+1-P_E))+1]$ *where* P_S *is the prevalence of smoking among pregnant women for which we use the national average of 12.2%.* P_E *is the prevalence of ETS exposure among nonsmokers which is 13.2%.* R_S *is the risk of LBW among smokers for which we use the estimate of 1.58 (Magee et al., 2004).* R_E *is the risk of LBW in ETS-exposed women relative to non-exposed for which we use 1.38. Substituting these values gives an attributable fraction of 4.1% and an estimated 1,347 excess cases of LBW. This calculation explicitly incorporates an estimate of maternal smoking during pregnancy which, unlike most states, California does not collect for its*

birth data. Use of the national average for prevalence of smoking during pregnancy of 12.2% is probably reasonable. However, if the actual smoking prevalence is lower in California, the number of LBW births attributable to ETS exposure will be higher and closer to the estimate presented in the document.

Comment 5:

Low Birth Weight: The Epidemiology

Clearly the RRs from your meta-analysis are factored into your Count.

The most notable thing, however, about all the selected studies, both the old and the 7 new, is that what they're all measuring -- each in its own way-- is lower birth weight, as importantly distinguished from Low Birth Weight, officially defined as 5.5 pounds or less.

As OEHHA reported in its first draft revision (6/9/97) the average Lowered Weight among the then-extant studies was a whopping 28 grams (or just shy of a single ounce.)! (p.20) What are we then to determine are the long-term, or even the short-term, health effects of a difference between a baby born at 6 pounds 7 vs 6 pounds 6? And whatever has this to do with Low Birth Weight and all its attendant risks?

Response:

Birth weight is a proxy measure for normal development. In the absence of other disease, decrements in birth weight reflect conditions in utero, from mildly to severely adverse. On a population basis, a decrement of 28 grams may be of little consequence. However, for the individual child this weight decrement may reflect developmental deficits that aren't rectified by the subsequent attainment of normal weight at a later date.

Comment 6:

Apparently not much. Not even among mothers who actively smoke:

> "The deficits of weight at birth of children born to mothers who smoked during pregnancy are overcome by 6 months of age. "
> - Conter et al, BMJ March 25,1995;320

In 1997, I had commented in detail on the underlying studies (seriously flawed) and OEHHA's conclusions (unwarranted, at best) as they appeared in the "final" February draft. I append those comments. And stand by them still.

Yet OEHHA, based only on the first round of studies (whose results it has now--but only now--come to admit "were also consistent with no effect," (p 3-36 of the current draft report) had nonetheless, at the time, made a bold statistical leap to RR 1.4 (a number only attained by omitting the negative findings of the largest summarized study) and concluded (on the gamble its

assumptions were all correct) that a body count could be had by playing games with the RR. (6/97)

I continue to find it odd that you were willing to count bodies in 1997 based on studies you now admit were con-sis tent with no effect but which you'd earlier characterized (p 3-35, Feb. '97) as "provid[ing] sufficient evidence that ETS exposure adversely affects fetal growth."

Point: Which is it? Are a series of flawed studies with weak and, even then, non-significant, results; with a lack of controlled confounders; no grip on misclassification; no trending of dose-response, and, yes, as you mention, "wide confidence intervals," whose subject, to begin with, wasn't even Low weight, but merely a missing ounce-- were they actualy "sufficient" to make a leap to an estimate of vast numbers At Risk? Or-- were they not? And if not (as you now suggest) why on earth did you count bodies on the basis of such dross? And why on earth should we trust you now?

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 7:

As for the 7 additional studies, they seem to be no better, at least not statistically speaking, and not enough detail is given to say more. ("Other" isn't enough information about confounders. Nor are we told much about the population of mothers.) And though, seemingly, the studies involved actual Low Birth Weight, as opposed to a missing ounce (?) one wonders about the studies that OEHHA didn't include, and the factors it didn't consider.

For example: After adjusting for active maternal smoking, there are the factors most highly associated with LBW:

Premature delivery:

> "'Ounce for ounce, the babies of smoking mothers had a higher survival rate.' [said Dr. Allen Wilcox, a researcher at the National Institute of Environmental Health Sciences.] Smoking may interfere with weight gain but does not shorten pregnancy. Thus, among smoking women, the smaller babies are more likely to be full term ...[I]t's prematurity not birth weight that explains higher mortality.."

-"High Infant Mortality in US Linked to Premature Births, " Jane Brody, New York Times, March 1, 1995

Low Socioeconomic Class

"the most powerful single risk factor."

-Redford et al, JAMA June 3, 1998:279.
Also Olsen et al, Ugeskr Laeger, Sept 19, 1994:156

Race:

"White infants were heavier and born later than black infants [even though] the white women in this sample smoked more cigarettes"

- Goldenberg et al, Am J Obs & Gyn, Nov., 1996:175

"The rate of Low Birth Weight is twice as high and the rate of Very Low Birth Weight is three times as high for black infants as compared to white infants."

-Luke et al, Int J of Gyn & Obst, March, 1993:40

Poor Nutrition:

"Smoking did not significantly affect infant birth weights." (after adjusting for nutrition.)

-Tchabo, Obst & Gyn, Sept, 1989: 74

"Data suggest that smokers in all social classes have a poorer quality diet."

- Haste et al, Am J Clin. Nutrition, Jan, 1990:51

Occupation:

"A greatly increased risk" for delivering underweight babies was observed among women who worked during their pregnancy. Especially for women required to stand on the job. Job stress, noise and irregular work schedules also increased the risk.

- Am J Obs & Gyn, Sept, 1995.

Other implicated factors:

(Again, after adjusting for active smoking.) Infections. History of induced or spontaneous abortion. First pregnancy after age 30. Medically induced fertilization. Single parenthood. Inadequate weight gain during pregnancy. Chronic illness. Caffeine consumption. Living at a high altitude, and poor dental health.

Response:

As noted in this comment, there are a number of factors that contribute to birth outcomes and perinatal survival. In addition, there is the paradoxical observation mentioned above that "Ounce for ounce, the babies of smoking mothers had a higher survival rate." This seeming paradox is an artifact of the common practice of calculating mortality rates based on the numbers of births occurring at any given gestational age or birth weight. It does not take into account the fact that birth weight is a reflection of the combined effects of fetal growth and the duration of gestation. A recently published analysis resolves this paradox by estimating perinatal mortality rates based on a "fetuses at risk" approach (Joseph et al., 2004) that better reflects the effects of the factors above on fetal and neonatal survival. In this analysis, the number of fetuses at risk of stillbirth at each gestational age were used to calculate gestational age-specific rates of stillbirth. A similar approach was used to calculate gestational age-specific perinatal and neonatal mortality rates.

Application of this technique to live and still births in the U.S. for 1997, stratified by maternal smoking status, showed that growth restriction rates were 1.5-fold higher among smokers than non-smokers at 32-33 weeks of gestation, and approximately 2-fold higher after 34 weeks. Gestational age-specific perinatal mortality rates were also higher among smokers than non-smokers for all gestational ages. In this study there is no evidence that offspring of smokers have a survival advantage at any weight or age. It is reasonable to conclude that the intrauterine environment created in association with maternal active smoke exposure adversely affects fetal growth and survival. Lower birth weight reflects restricted intrauterine growth and/or premature birth, and as such is a proxy measure for increased risk of infant mortality. Indeed, it was associated with increased perinatal mortality among infants of smokers in this study. While this study did not address passive smoking, the association of ETS exposure with lower birth weight and low birth weight is expected to similarly reflect increased risk of mortality.

Comment 8:

Surely, not all of these confounders were adjusted for, if indeed such adjustment is actually possible

> "People ... say they'll use statistics to make adjustments for biases and incompleteness. I've spent more than 20 years working as a statistician and I can assure you that you cannot use statistics to adjust."
>
> Dr. Richard Doll, New York Times, Aug 9, 1994

Then, too, since exposure to smoking has gone down, one might as easily postulate, given the economy, that more women are working (and standing on their feet), or more women are under stress. Or can't afford to go to the dentist. Each of these hypotheses is no less of a reach than fingering ETS, and especially in an era when exposure has declined.

Almost needless to say, I find the rest of your figures in the referenced Table to be equally suspect.

Surely you're aware of the unusual method of reckoning that was used by the EPA to arrive at its estimate of 3,000 lung cancer deaths from ETS. A method that included using recently "former" smokers, assumed that any/ ever exposure was a Risk, and was mainly based on questionable epidemiology on the lifelong spouses of smokers.

Now, climbing on top of that, OEHHA appears to estimate that virtually all lung cancer deaths among non-smokers are caused by ETS!? It hardly pays to ask upon what this is based.

So, too, for the climbing levels of heart disease death you now attribute to ETS. In 1994, the Congressional Research Service called the then-current estimate of 37,000 to be, in a word, "implausible." The escalated Number of 69,000+ is, if anything, doubly implausible.

However, you'll get what you're after from this report, --headlines from an ever-credulous media

I understand the futility of attempting to comment, but conscience compels it.

(Low Birth Weight Studies Con't)

I read (in amazement) the first 35 of these incredibly sloppy studies. (P 3-1 to 3-15). The first thing that hit me was the overwhelming waste--waste of money and waste of time --in the hot pursuit of a fictive grail.

All of these studies had disqualifying flaws. Most predominantly: no confounders accounted for. Or big ones not accounted for. (Maternal height and weight; or socio-economics; or working status of mothers--an independent risk, see ** below.) And none appeared to control for such common-sensical factors as the pregnant woman's diet; or alcohol consumption; or vitamin supplementation.... or several other bigs. Confounders that were tested for were usually not listed; nor were numbers frequently given. And a number of other factors were "expected" or "assumed" or "considered to" or "thought to" but not apparently proved.

Then too we get this: very little or no statistical significance and no dose-response (or irrational dose/response), the inclusion of smoking mothers, plus the contradictory data--both between and within--all the individual studies.

Then back to semantics. Negative (or seemingly protective) effects are elaborately rationalized and swept under the rug. (eg, M.acArthur and Knox; Ahlborg and Bodin; Zhang and Ratcliffe) whereas nothing at all's said about the positive (or otherwise inculpatory) anomalies in most of the other studies. And the use of deformed children only may effect the results

Your conclusion thus baffles "All but one of the studies on the impact of ETS exposure in the home... found a decrement in mean birthweight." Underwood et al (0.9 for any paternal smoking), MacArthur and Knox (a 100 gram excess) Yerulshalmy (1.0 among nonsmoking mothers) Mahtai et al ("no difference in the rates of LBW by mother's ETS exposure).

Is that one or is it four? And that's granting all the stuff that's statistically non-significant (which, as it happens here, is most of the stuff you've got.)

Are you daunted? Uh-UH. You conclude (by projection) from egregiously flawed studies which--if accepted, yield statistical "never-mind"-- that the RR attributable to ETS exposure is "1.2 to 1.4" which you then procede to quantify. Endowing us with images of thousands of scrawny babies left bellowing in their cribs.

This is actually shameful.

- "Comment on OEHHA Assessment of ETS," Stewart, April 28, 1997. From original document.

Response:

It is clear that there are a number of confounding factors that influence birth weight. It is also clear from the body of evidence in the epidemiological literature that ETS is one of those factors. The commentator believes the effect of ETS can be explained away but does not provide a clear and compelling argument substantiating the assertion. The implication is that most studies did not account for confounding factors or did not have statistically significant results. While no epidemiological study is perfect, many of the studies did in fact account for specific known confounders. Some of the studies in and of themselves which controlled for confounders were statistically significant (e.g. Jedrychowski and Flak, 1996; Kharrazi et al, 2004, Dejmek et al, 2002). In addition, two meta-analyses provided pooled estimates of decrements in birth weight that were statistically significant (Windham et al., 1999, –24.0 g (95% CI –39.3; -8.6) and Peacock et al., 1998, - 31g (95% CI –44;-19)). Thus, while there are typical problems with some of the epidemiological studies and many show a decrement in birth weight that is not statistically significant, taken together in these two meta-analyses, the studies provide strong evidence of an adverse effect of ETS exposure on birth weight.

References cited in responses:

Centers for Disease Control (CDC) (2001). National Report on Human Exposures to Environmental Chemicals, Centers for Disease Control and Prevention, Atlanta, GA Pp.33-34.

Centers for Disease Control (CDC, 2002). National Center for Health Statistics. Table E. Number of infant deaths, percent of total infant deaths, and infant mortality rates for 2000, and percent change in infant mortality rates from 1999 to 2000 for the 10 leading causes of infant death in 2000: United States. National Vital Statistics Report 50 (15): 13. (Chapter 1)

Centers for Disease Control (CDC) (2003). Second National Report on Human Exposures to Environmental Chemicals, Centers for Disease Control and Prevention, Atlanta, GA Pp. 79-80.

Dejmek, J.; Solansky. I; Podrazilova, K., and Sram, R. J. (2002). The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. Environ Health Perspect. 110(6):601-6.

Jedrychowski W, Flak E (1996). Confronting the prenatal effects of active and passive tobacco smoking on the birth weight of children. Cent. Eur. J. Pub. Health 4:201-5.

Joseph KS, Demissie K, Platt RW, Ananth CV, McCarthy BJ, Kramer MS (2004). A parsimonious explanation for intersecting perinatal mortality curves: understanding the effects of race and of maternal smoking. BMC Pregnancy Childbirth 4(1):7.

Kharrazi M, DeLorenze GN, Kaufman FL, Eskenazi B, Bernert JT, Graham S, et al. (2004). Influence of low level environmental tobacco smoke on pregnancy outcomes. Epidemiol. In press.

Magee, B. D.; Hattis, D., and Kivel, N. M. Role of smoking in low birth weight. J Reprod Med. 2004 Jan; 49(1):23-7.

Peacock JL, Cook DG, Carey IM, Jarvis MJ, Bryant AE, Anderson HR, et al. (1998). Maternal cotinine level during pregnancy and birthweight for gestational age. Int J Epidemiol 27(4):647-56.0300-5771

Windham GC, Eaton A, Hopkins B (1999). Evidence for an association between environmental tobacco smoke exposure and birthweight: a meta-analysis and new data. Paediatr Perinat Epidemiol 13(1):35-57.

Comments of Michael J. Thun, M.D. (on behalf of the American Cancer Society, Atlanta, GA)

Comment 1:

The California Environmental Protection Agency (Cal/EPA) is to be commended for its comprehensive review of the scientific literature on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (1). This update of a previous Cal/EPA monograph (2) adds valuable information on the extensive clinical and experimental evidence regarding ETS and heart disease from studies published since 1997. It is notable that the previous Cal/EPA report was the first to draw widespread attention to the adverse cardiovascular effects of ETS exposure. This relationship is now well established, due in part to the groundbreaking contributions of Cal/EPA.

Response:

Thank you for these supportive comments, and for the thorough review and analysis of the document, in particular our evaluation of studies on the association between breast cancer and exposure to ETS. OEHHA staff was gratified to see the positive reception that the 1997 document received, and hope that the present update will prove similarly useful in promoting public health and scientific understanding of the effects of ETS.

Comment 2:

The current draft report concludes that ETS exposure is causally related to cancers of the lung, breast, and nasal sinuses (Page 7-1). The relationship between ETS and breast cancer is said to appear stronger for pre- than post-menopausal breast cancer. In this report, Cal/EPA again distinguishes itself by providing an update of the evidence on ETS and lung cancer, and by drawing attention to the accumulating evidence concerning breast cancer and second hand smoke. However, the conclusions of this report with respect to breast cancer conflict with that of a working group of the International Agency for Research on Cancer (IARC) (3). IARC characterized the evidence regarding ETS and breast cancer as "inconsistent". The conclusions of Cal/EPA and IARC also differ with respect to cancers of the nasal cavity and paranasal sinuses. Both the current and previous Cal/EPA report include cancer of the nasal cavity as causally related to ETS. IARC lists cancers of the nasal cavity and paranasal sinuses among the 15 cancer sites caused by active smoking, but does not designate either of these cancers as causally related to ETS.

Response:

There are a 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 that were unavailable to IARC at the time of their report. OEHHA staff and consultants also undertook different (and more extensive) analyses of data and metadata than those used by IARC. Even where the data

considered are the same, different experts may reasonably come to differing conclusions. Details of the Cal/EPA report's conclusions in relation to breast cancer are discussed in subsequent responses. The conclusion in relation to cancer of the paranasal sinuses is also clarified in response to specific comments by Dr. Thun.

Comment 3:

The question of whether ETS, or more generally tobacco smoke, causes breast cancer is extremely important. If passive smoking does cause breast cancer, then policies that reduce ETS exposure will help to prevent this cancer and will strengthen the social mandate to protect non-smokers from second-hand smoke. However, if the evidence is not conclusive at this time, then a premature decision about causality could jeopardize the credibility of the entire review process. The current evidence that ETS exposure causes lung cancer and heart disease is convincing. It is crucial that other conditions be added to this list only if the evidence supporting a causal relationship can withstand careful scientific scrutiny.

Epidemiologists at the American Cancer Society (ACS) (Thun, Henley, Oltmanns, and Calle) have carefully reviewed the sections of the report pertaining to breast and nasal sinus cancers. We evaluated this evidence in relation to the Cal/EPA criterion that "chance, bias, and confounding can be ruled out with reasonable confidence" (page 1-9). At present, we do not believe that the published evidence meets these criteria for cancers of the breast or nasal sinuses, although we do believe that breast cancer in particular is an important topic for continuing research. We offer the following comments for consideration.

Response:

We thank Dr. Thun for his critical comments on our evaluation of the association between breast cancer and ETS exposure, and our conclusion of a causal association based on both epidemiological evidence and supportive data from the animal toxicology literature on specific constituents of tobacco smoke. We agree that the conclusion in relation to breast cancer and smoking is extremely important. We consider that the "credibility of the review process" is equally jeopardized by a premature decision in favor of causality, and by a failure to respond to new and important findings and analyses, which support that conclusion. We have received a number of comments about this conclusion, some supportive and some not. Having carefully reviewed the thoughtful comments by Dr. Thun and others (see below, and in other sections of the responses to comments) we stand by the conclusion expressed in the draft report, that the existing evidence suggests that the association between ETS exposure and increased incidence of breast cancer may reasonably be considered causal. As an agency charged with a responsibility for the health of Californians, it would be equally detrimental (perhaps far more detrimental in terms of public health) to fail to inform the public of a risk where the evidence of an effect is credible and meets our criteria for causality.

General Comments

Comment 4:

1) The summary of the epidemiologic evidence concerning breast cancer (pages 7132 to 7-147) offers four hypotheses, listed below, to explain why published studies of active smoking and/or ETS exposure have not consistently found increased risk of breast cancer risk in exposed women. However, the discussion of this evidence, in terms of its consistency, strength and specificity, and limitations, is relatively brief. This section needs to be expanded and broadened to assess systematically the extent to which published studies support or conflict with the hypotheses proposed. It also needs to consider other potential limitations of case control studies, particularly biases that may be introduced by the use of highly selected reference groups.

Response:

The hypotheses that have been put forward by various authors and briefly presented in the review are considered to be just that, hypotheses. These indeed are supported by findings in various studies and as Dr. Thun mentions below are biologically plausible. We have not attempted to prove these or quantify the level of supporting evidence, as that is beyond the scope of our work. Since they are considered hypotheses their disproof would not be evidence that the data found in the epidemiologic studies in question are wrong, but merely that there is a different reason for the results. However, we do provide further analysis of these questions in these responses to comments, and in the revised version of the final document, insofar as they are helpful in developing and testing our conclusions with regard to the associations between exposures to tobacco smoke and breast cancer.

In the final sentence, the identification of highly selected reference groups as a potential source of bias is taken as referring to the fact that the referent exposure category "never exposed to ETS" constitutes a relatively small subgroup (as Dr. Thun notes later, 10% of non-smokers in Johnson 2000) of the total sample of non-smoking women. It is inappropriate to describe the identification of these referent individuals as "selection" in the sense usually employed since they represent all members of the sample population having the specified data value. Any underlying differences in their characteristics relative to the study sample as a whole would arise not from selection bias but from the existence of other exposures or characteristics that are highly correlated with the status of non-smoker not exposed to ETS, which also influence disease outcome. The most likely factor to fit in that category would be alcohol, which has been controlled for as an independent variable in most of the studies in question. Neither Dr Thun's comments nor OEHHA's review have identified other major confounding variables which have been consistently ignored in the study designs. The alternative to use of this referent group would be to knowingly misclassify some percentage of the 90% (Johnson, 2000) of non-smokers who are exposed to ETS as nonexposed. In studies where only 10% of subjects are exposed to a factor (for example occupational studies), researchers do not doubt results because this is "highly selected group" but rather control for known risk factors and report the results they

observe. It seems curious to worry about refining the control group to mean not-ETS exposed as som how different.

Comment 5:

2) The hypotheses proposed to explain the lack of association between breast cancer and active and/or passive smoking can be paraphrased as follows (page 7-133):

Response:

OEHHA thanks Dr. Thun for his thoughtful analysis of this issue. However, the paraphrase presented in the following comments does to some degree mischaracterize the hypothesis that OEHHA chose to evaluate. Individual responses given below will attempt to address this, and it is hoped that the fuller description inserted into the revised document will remedy this evident lack of clarity for future readers. OEHHA has also taken the opportunity in revising the document to include references to some additional papers that have appeared in the scientific literature after the preparation of the public review draft (and, in some cases, after the comments received were written).

Comment 6:

a. The dose-response relationship between exposure to tobacco smoke and breast cancer risk may be non-linear. According to this theory, low doses of tobacco smoke (such as result from ETS exposure), may increase risk, whereas higher doses (such as those due to active smoking) may obscure this risk, because of the anti-estrogenic effects of active smoking. This theory is proposed to explain why ETS may increase breast cancer risk, even though active smoking does not.

Response:

OEHHA prefers to characterize the non-linearity of the dose-response for breast cancer to tobacco smoke as an observation rather than a theory. 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 active smoking does not increase breast cancer risk. In order to explain the essentially null results of Wartenberg et al. (2000), 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 7:

b. Tobacco smoke may increase breast cancer risk only in a genetically susceptible subgroup of women. This theory suggests that studies that combine all women and do not stratify on genetic susceptibility may obscure an association.

Response:

There are a number of studies that suggest that this may be an important consideration. It should be noted that there is likely not one single genetically susceptible subgroup, but a wide range of such groups depending on the polymorphism of several genes, which are hypothesized to be important in the metabolism of various tobacco-related carcinogens (Vineis et al., 1994). Also, the relationship is further complicated by the fact that interactions between metabolic status, level of exposure, age at exposure, and estrogen levels may occur, such that some subgroups may only show differential responses at certain (e.g. lower) doses or depending on pre- or post-menopausal status. These complexities may account for the different results seen in such studies, which should be characterized as diverse rather than conflicting.

Comment 8:

c. Human breast tissue may be vulnerable to exposure to tobacco smoke only during certain critical time periods. For example, vulnerability may be greatest between menarche and first pregnancy, as is the case with ionizing radiation. Epidemiologic studies that define ETS exposure in other ways (such as years of childhood exposure, cumulative exposure, or continuing exposure) may misclassify the biologically relevant exposure and thus fail to detect a real association.

d. Tobacco smoke may affect certain types of breast cancer but not others. For example, some studies have reported increased risk only in relation to premenopausal breast cancer.

Response:

The document lists a number of studies where age-related differences in sensitivity to tobacco smoke appear to produce differences in response to either active or passive smoke exposures. OEHHA has noted these observations and attempted to incorporate them into the overall explanatory hypothesis, as the commenter notes. Related to this point is that prospective cohort studies, in addition to having difficulty ascertaining exposure over a long time period by asking questions in the beginning of the study about largely spousal exposure to ETS, do not ascertain childhood exposures well if at all. The subjects need to remember back to childhood to provide responses about childhood exposure (which were not even asked in most of the cohort studies. Thus, peri-pubertal exposures are poorly ascertained. Most peri-pubertal exposures are largely to ETS and not mainstream smoke. The different chemical constituents (higher PAH and carcinogenic amines in sidestream than mainstream smoke) results in different exposures peripubertal relative to older children and adults. This too complicates the picture and may be

another reason that it is difficult for prospective cohort studies to find an effect of ETS on breast cancer.

OEHHA does not argue, as implied in point 2d, that tobacco smoke affects only certain types of breast cancer but not others, nor was it suggested that there is a systematic difference between pre-menopausal and post-menopausal cancers. (OEHHA is aware that cancers diagnosed after menopause on average show a lesser degree of estrogen dependence, but surely this reflects selection during the progression phase rather than any necessary differences in the initial causation, which in either case probably occurred many years previously.) In summary, OEHHA is assuming a difference in sensitivity with age and developmental status of the breast [as delineated for instance by Lash and Aschengrau (1999)] – i.e. differences in the breast rather than the cancer caused. Differences between cancers may or may not exist, but this is not a part of the hypothesis under discussion.

Comment 9:

3) Any or all of the above hypotheses are biologically plausible. However, the hypotheses themselves do not constitute evidence that active or passive smoking causes breast cancer. Additional evidence supporting these hypotheses is particularly necessary because of the large published literature that shows no overall relationship between active smoking and breast cancer. As noted by IARC; "the lack of an association with active smoking weighs heavily against the possibility that involuntary smoking increases the risk of breast cancer, as no data are available to establish that different mechanisms of action are in play at the dose levels of active and involuntary smoking." In revising the report, Cal/EPA should systematically examine which studies (basic, epidemiologic and other) support each hypothesis and which do not. The following points, in particular, need attention.

Response:

As detailed below, and in the revised document, OEHHA disagrees with the assertion in this comment, and in the IARC review, that there is no association between active smoking and breast cancer. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of spousal smoking habit as a sole, dichotomous measure of ETS exposure seems egregiously inadequate since it largely fails to capture the extent of exposure during the period of greatest sensitivity. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship (typically, faute de mieux), in this case this assumption is neither necessary, nor supported by the data.

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 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. The existence of a mammary carcinogenic effect of tobacco smoke is supported by numerous studies of its individual components, which include several IARC-recognized human carcinogens. Additionally, there are several explanatory hypotheses which can be advanced, with varying degrees of experimental and epidemiological support, for the non-linear dose response relationship. The existence of such plausible mechanistic hypotheses certainly provides support for OEHHA's analysis, but it is not necessary that any or all of these mechanistic hypotheses be proven beyond doubt; the key assumption of causality and non-linear dose response precedes the explanatory hypotheses rather than being derived from them.

Comment 10:

a. The report should acknowledge that extensive epidemiologic data shows no overall association between active cigarette smoking and incident breast cancer, in analysis that include women exposed to ETS in the referent group. A meta-analysis of 53 epidemiological studies found that, among 22,255 women and 40,832 controls who drank no alcohol, there was no overall association between active cigarette smoking and breast cancer [RR=0.99 (95% CI=0.92-1.05)] (Figures 1 & 2) (4). All of the studies in this analysis had individual information on reproductive risk factors for breast cancer and hormonal therapies with which to control for these factors. Alcohol consumption was unequivocally associated with breast cancer in these studies and correlates strongly with active smoking (and possibly with ETS exposure). Therefore, it is essential that studies of active or passive smoking in relation to breast cancer be able to control for alcohol consumption, which some have not.

Response:

The above mentioned meta-analysis makes no claims of considering in any way passive smoke exposure. Under the methods section they state that "no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure". If, as we believe to be true, the data supports a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason) and if most non-smokers have had significant ETS exposure which is certainly the case, particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk. In effect, the analysis is to a large degree comparing exposed with exposed.

Reynolds et al. (2004) in their recent prospective study, which at your suggestion we have added to the report, did find a significant association between active smoking and breast cancer that increased with increasing duration and intensity of smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated

risk of breast cancer (HR 1.66, 95% C.I. 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure.

An interesting paper by Zhang et al. (2004) has been published as an abstract since the initial draft of our document and will be included in the discussion. In that cohort study of 49,165 Canadian women aged 40 – 59 were followed for 14 years: Women had an elevated risk of breast cancer death if they had smoked 30 years or more (HR = 1.90;95% CI, 1.29, 2.80), compared to never smokers. When compared to nondrinkers who had never smoked, light to moderate drinkers (>0 and <20 g/day of alcohol) who smoked for more than 30 years were twice as likely to die of breast cancer (HR = 1.98; 95% CI, 1.13, 3.48). Heavy drinkers (20+ g/day of alcohol) who smoked this long had almost a three-fold risk of breast cancer death (HR = 2.72; 95% CI, 1.30, 5.67). Heavy drinkers who smoked 40+ cigarettes/day experienced an almost four-fold risk of breast cancer death (HR = 3.85; 95% CI, 1.34, 11.09). There was a positive dose response relationship between years smoked and breast cancer mortality ($p<0.05$) among both drinkers and non-drinkers, after adjusting for cigarettes per day smoked, alcohol consumption, and other potential confounders. Apparent in this study is an at least additive effect of alcohol and smoking and an effect of smoking independent from drinking. We agree with the commentator's suggestion that it is very important to control for alcohol consumption and have weighed our consideration of studies accordingly. Though not always clearly identified in the individual papers as such, many of the recent studies do include control for alcohol consumption. We have made additional notations in the OEHHA document to clarify where papers have considered alcohol consumption in the revised document.

Comment 11:

b. At least six studies of active smoking and breast cancer have examined the association with and without exclusion of ETS exposed women from the referent group (Figure 3). Four of these studies show some increase in the relative risk (RR) estimate when ETS women are excluded (Morabia 1996, Johnson 2000, Kropp 2002, Egan 2002) while two show either no increase (Marcus 2000) or a decrease (Reynolds 2004). In no study is the effect of this exclusion statistically significant. The increase in the relative risk estimate resulting from the exclusion appears to be larger and more consistent in the case control studies than in cohort analyses, raising concerns about potentially biased reporting of exposure in retrospective studies. At least five case control studies featured in the Cal/EPA report (Sandler 1985, Morabia 1996, Lash 1999, Johnson 2000, Kropp 2002) and one prospective study (Reynolds 2004) found an association between active smoking and breast cancer incidence, even when they did not exclude ETS exposed women in the referent group. The observed association is so strong in two studies (Sandler 1985 & Morabia 1996), that if it were real, some increase in risk would be apparent in most studies of active smoking, irrespective of methodological differences. Cal/EPA needs to address the potential for biased reporting of exposure in case-control studies in the section on "Limitations of studies (7-139 to 7-140), and possibly in the summary on page 7-147.

Response:

Thank you for providing the attached figures. Figure three is, however, somewhat confusing to us. It is labeled as "breast cancer among current active smokers…" though in Johnsonet al. (2000) the data for this analysis of the effect of inclusion or exclusion of passive smokers in the referent is given for "ever smokers". In Morabia et al., (1996) the data is also for "ever smokers" and is given for three levels of exposure that cannot be combined without the raw data. Using only one level's data will give a wide confidence interval, as the selected population will be relatively small. While Kropp and Chang-Claude's data is for current smokers, it would clearly be more appropriate, and provide tighter confidence limits, if current and former smokers were combined for an index similar to the other studies "ever smoker" category. In a qualitative way, we believe that this figure does make a point that a lifetime exposure history is important to consider. The four case-control studies that show an increase in ORs are studies with measures that include different life-stages as well as assessment of home, occupational and other exposures. The two cohort studies that do not find a difference (or even a slight decrease) are ones in which important measures were not collected.

Although Figure 3 provides a nice graphical representation of the effect of removing subjects with passive smoke exposure from the control groups, it cannot be used to make a statement about the "statistical significance" of the effect of the exclusion. Excluding subjects with passive smoke exposure sharply reduced the sample size in most of the analyses presented. This has the effect of increasing the standard error of those estimates and increasing the size of the confidence intervals. This makes the difference harder to detect. However, overlapping confidence intervals do not imply that two odds ratios are not statistically different. A general rule of thumb states that "confidence intervals associated with statistics can overlap as much as 29% and the statistics can still be significantly different" (van Belle G., 2002). This is true because the standard error of the difference between two statistics is smaller than the sum of the individual standard errors. Therefore, the odds ratios from the Johnson et al. (2000) study may actually be statistically different, since a reduction of the confidence intervals by 29% would cause them to not overlap. Many authors perform "sensitivity" analyses with their data to see whether their results are robust to changes in definitions of disease, definitions of exposure, and restriction to subgroups of subjects. In many cases, these analyses have reduced power. However, they are used as a qualitative measure of robustness, and authors do not make statistical comparisons between estimates obtained from the sensitivity analyses. Therefore, Figure 3 should be used as a qualitative illustration of the effect of removing passive smoke exposure from the control groups.

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 cigarette smoke hypothesis was the main purpose of the study, 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/ETS smoking was among a long list of questions, it is unlikely that bias would have occurred. In response to this comment 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.

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

Smith et al. (1994). The data for this study derived from the UK National Case-Control Study Group that was designed to investigate the relationship between contraceptive use and breast cancer. Data were also collected on other lifestyle factors such as smoking by interview. However, information on passive smoke exposure was obtained via a self-completed questionnaire returned by mail, thus minimizing interviewer bias but the possibility of recall bias remained.

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 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 ever-passive smoking would still be significant (1.8, 1.2;2.8). The Morabia study did suggest increased risk beyond what you would expect for active smokers compared to never smokers. This may indicate that the sampling had an excess of smoking cases or a deficit of smoking controls, and that passive and active risks may be higher than one would expect for passive smoking and passive-controlled active smoking (as was the case compared to the other ETS-breast cancer studies), but not that there would be no risk.

Millikan et al. (1998). This study was also based on the CBCS (see Marcus) and so used interviews by trained nurses. Little information was presented to assess possible bias. They did note that smoking prevalence among controls was 20%, similar to a recent survey conducted among women in North Carolina. Thus a positive association between smoking and BC is not due to high refusal rates (for interviews or blood draw) among controls who were smokers.

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 could have occurred. "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 causes cancer may contribute to some disease-dependent recall of exposure to tobacco smoke."

Johnson et al. (2000). Questionnaires were mailed, thereby eliminating interviewer bias. ETS questions were among many others on breast cancer (BC) risk factors. Data from subjects with one of 18 other cancers, including a large sample of lung cancer cases, were also collected in the same data collection (the National Enhanced Cancer Surveillance System). Possible recall or response bias was examined by comparing 71 never smoking women with lung cancer and 714 never smoking women controls, the same pool of controls used for the breast cancer analysis. They found an age-adjusted OR of 1.2 (0.7; 7.1) for the association between lung cancer and years of home ETS. More recent meta-analysis 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 BC risk estimate. Furthermore when Johnson et al. examined the risk of active smoking in the traditional way (ignoring ETS exposure) the observed risk was 1.0 for premenopausal breast cancer and 1.2 for postmenopausal breast cancer, consistent with the literature.

Delfino et al. (2000). Data were collected by interview of women scheduled to receive breast biopsy to rule out mammary carcinoma. Prior to biopsy, women took a self-administered questionnaire on risk factors. The study included only subjects whose questionnaires were returned by mail prior to receiving diagnosis. Eligible patients, participants and interviewers were all blind to case/control status. Interviewer and reporting bias were thus minimized. Participation rates were similar between those with and those without a diagnosis of cancer.

Morabia et al. (2000). This was a population-based study presented to participants as an on-going survey of women's health, the aim of which was not specified. Trained interviewers were blind to case/control status. Interviewer and reporting bias appear to have been minimized in this study, but recall bias was not specifically addressed. However, this study appears to be based on the same group as Morabia et al (1996), so presumably the same bias controls apply.

Marcus et al. (2000). This was a population-based study (Carolina Breast Cancer Study, CBCS). Interviews included administration of standardized questionnaire that covered established and suspected risk factors. Interviewer bias can't be ruled out. Authors report that response rate varied by age and race, however, stratification by age and race subgroups gave ORs similar to main group. They suggest that differential recall between cases and controls regarding adolescent smoke exposure was unlikely since an association between adolescent smoke exposure and BC is not generally perceived. On the other hand, the authors acknowledge

that misclassification is likely regarding the timing of thelarche vis-à-vis smoke exposure but they suspect it would be non-differential.

Krajinovic et al. (2001). Data were collected by interview in an earlier breast cancer study. Smoke exposure was one of several risk factors characterized as part of a study of gene-environment interactions. Without a more complete description of the original study, it's difficult to assess the potential biases at work in this study.

Kropp and Chang-Claude (2002) used self-administered initial questionnaires (so no interviewer bias at this stage) on BC 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."

Band et al. (2002). Mailed questionnaires investigated occupational risk factors of which smoking history was a small part, so no interviewer bias was involved. The study was population-based with a high response rate thus minimizing selection bias. In addition, the proportion of never- and ever-smokers was similar among responders and non-responders for both cases and controls. However, the information for non-responders was obtained for only small subsets. The authors claim that recall and misclassification of age at commencement of smoking was not likely to systematically differ between cases and controls since smoking was not generally perceived as related to breast cancer. The absence of information on passive smoking could have led to misclassification of passive smokers as non-exposed but this would bias towards the null.

Lash & Aschengrau (2002). Data were collected by trained interviewers on demographics, smoking history and other risk factors. The only information in the paper regarding potential bias is: "Given that smoking history and history of residential passive smoke exposure should be well recalled, and given that an earlier investigation using a similar survey and population yielded causal results, we doubt that non-differential misclassification of exposure status accounts for the null results reported here."

Shrubsole et al. (2004). In this population-based case-control study, data on demographics, health, activity, diet, and ETS exposure were collected by trained interviewers. The use of structured questionnaires is the only study feature mentioned in the report that may have limited interviewer bias. While reports of lifetime ETS exposure excluded childhood exposure, recall bias is still a possibility. Assessment of workplace ETS exposure was limited to the preceding five years but assumed to reflect longer-term exposure. However, this assumption was not verified. Selection bias is thought to have been limited by the population-based design and the high participation rate (91.1%).

Comment 12:

c. Perhaps the most critical factor not considered by the Cal/EPA report is the potential for bias in studies that exclude women with any exposure to passive smoking from the referent group. This is particularly problematic in case control studies where women recall their ETS exposure retrospectively, already knowing whether they have breast cancer. Most women in Western countries who are old enough to develop breast cancer have had substantial past exposure to ETS. The subgroup of women designated as never-active, never passive smokers comprises a small percentage of all never-smoking women (about 10% in the study by Johnson et al., 2000). Reliance on a small and highly selected referent group may introduce serious problems with both the validity and statistical precision of these studies. In general, the published studies do not provide information about the demographic and behavioral characteristics of women in the referent group who report neither active nor passive smoke exposure. Reliance on a highly selected control group may introduce more biases than it removes.

Response

In the final sentence, the identification of highly selected reference groups as a potential source of bias is taken as referring to the fact that the referent exposure category "never exposed to ETS" constitutes a relatively small subgroup (as Dr. Thun notes, 10% of non-smokers in Johnson 2000) of the total sample of non-smoking women. It is inappropriate to describe the identification of these referent individuals as "selection" in the sense usually employed since they represent all members of the sample population having the specified data value. Any underlying differences in their characteristics relative to the study sample as a whole would arise not from selection bias but from the existence of other exposures or characteristics that are highly correlated with the status of non-smoker not exposed to ETS, which also influence disease outcome. The most likely factor to fit in that category would be alcohol, which has been controlled for as an independent variable in most of the studies in question. Neither Dr Thun's comments nor OEHHA's review have identified other major confounding variables which have been consistently ignored in the study designs. The alternative to use of this referent group would be to knowingly misclassify some percentage of the 90% (Johnson, 2000) of non-smokers who are exposed to ETS as nonexposed. In studies where only 10% of subjects are exposed to a factor (for example occupational studies), researchers do not doubt results because this is "highly selected group" but rather control for known risk factors and report the results they observe. It seems curious to worry about refining the control group to mean not-ETS exposed as some how different.

It is a feature of many epidemiologic studies that comparisons are made to groups representing relatively small minorities of the general population. In the study that Dr. Thun cites above as important (Collaborative Group on Hormonal Factors in Breast Cancer (2002), those with no alcohol consumption are utilized as the referent and the paper draws the earlier cited conclusion that alcohol is directly associated with breast cancer (and not smoking). The demographic characteristics of those women in the combined 53 studies are not well defined.. They (particulary the heavy drinkers) might be considered a highly selected exposure group by these proposed standards. In the California Teachers prospective cohort (Horn-Ross P, et al. 2002)

only women with 20 grams of alcohol intake/day or greater showed a significant increase in risk for breast cancer. At least in that California cohort those with 20 grams or more intake comprise only 8% of all women. In addition, in further analysis of the California Teacher's cohort Reynolds et al. (2004) found that among never smokers, those with increasing alcohol consumption were much more likely to be exposed to ETS (5-15 gm/day OR for ETS exposure= 1.70: 95% C.I. 1.61-1.80). If as we propose, ETS is a causative factor in development of breast cancer, the increased exposure to ETS in drinkers may account for a portion of the observed association with alcohol. Any study that characterizes participants in quartiles or quintiles selects only 20 or 25% of the potential population as a control group. The studies that utilize women non-smokers not exposed to ETS have been conducted in numerous countries throughout the world. Certainly in some Asian studies non ETS exposed is not a small minority of women non-smokers. We do not see any indication that there is likely some unmeasured factor related to the disease that is disproportionately present (and not already controlled for) in a non-ETS exposed control group that would preclude it's selection as a comparison population.

In the group of studies that look at ETS exposure and breast cancer there is a wide range of values for the percentage of referrents who are "unexposed" to ETS due to the various methods of defining unexposed as well as characteristics of the populations studied. Only Johnson, Egan, and Smith have case or control percentages of unexposed below 20%. In the Johnson study, the pre-menopausal group had only 6% of the cases unexposed, and 15% of the controls. However, when they added those whose exposure was up to ten years to the referent group (in order to stabilize the estimates), the OR for more than 10 years of exposure became 2.0 (95% CI, 1.2-3.3), and with this expanded definition, case non-exposure became 17%, and control non-exposure 29%. Even with a less precise but larger referent, the OR is still high and even more statistically significant. Below is a chart of the percentages of non-exposed cases and controls in various studies that evaluate passive smoke exposure and breast cancer. Most of the studies that broke out those controls not exposed to ETS report a larger percentage of the control group as not exposed than the 10% figure from Johnson et al. 2000 cited in the comment.

Study	**Cases not exposed to ETS**	**Controls not exposed to ETS**
Hirayama (1984)	20%	24%
Sandler	41%	57%
Smith	5%	13%
Morabia	22%	39%
Milikan	36%	35%
Lash 1999	34%	33%
Delfino	52% (low risk pool)	73% (low risk)
Zhao	35%	56%
Jee	No data available (NDA)	NDA
Johnson	11%	17%
Nishino	70%	58%
Kropp	22%	32%
Lash 2002	26%	21%
Egan	9.8% (low risk)	NDA

Comment 13:

d. In summarizing the epidemiological evidence (pages 7-132 to 7-139), Cal/EPA should acknowledge that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure. These studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer. In at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. The prospective data should be considered far more seriously in weighing the totality of the evidence than has been the case in the current draft.

Response:

We have indicated more clearly that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure, that these studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer; and that in at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. Although cohort studies in general have the potential to be preferable for examination of risk, all three of these studies suffer from seriously incomplete measures of passive smoking exposure. The ability to determine a risk associated with ETS exposure and lung cancer and cardiovascular disease in the ACS and Harvard Nurses Cohorts but not find a risk for breast cancer may result from various factors. Cardiovascular disease is very sensitive to more recent exposure (Whincup et al., 2004) and therefore less complete historical data may be less of an impediment than for breast cancer. Exposures during the critical period of susceptibility between onset of adolescence and delivery of first baby, a period of rapid proliferation and differentiation of breast cells of the lobules and ducts and a known period of increased sensitivity to carcinogenisis, are likely to be of special importance to the risk of development of breast cancer. These windows of susceptibility present a substantially different picture than for lung cancer for which the data indicate a very linear dose response. The data collected by these studies may more closely reflect the important exposure in the case of lung cancer than in the more complicated scenario of breast cancer. The potential impact of this serious shortcoming in exposure measurement is addressed by Hertz-Picciotto (1998) and were addressed in the earlier draft for the first two studies and in the revised draft for the Reynolds paper. A fundamental requirement for study validity is a level of accurancy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all important measures of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontham et al. (1991,1994), which is indeed a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements for exposure assessment.

While it is true that, in the prospective studies exposure is ascertained prior to disease onset and that this is a desirable feature, exposure during the critical period of adolescence and young adulthood is obtained by retrospective history since enrollment is typically well beyond that time in life. In this case, the exposure history in case-control and prospective studies suffer from the same drawbacks. The problem of reporting bias related to retrospective studies is mitigated as the potential link of smoking or ETS to breast cancer is not commonly known to the public.

An example of the importance of adequate exposure history is found in a paper by Eisner et al. (2001). Many studies, including both prospective and case-control studies, utilize a form of yes/no questioning of spousal smoking habits to determine exposure. In other words, exposed is often determined by the question, "does your spouse smoke?" with no consideration of smoke exposure in childhood or in adult workplace or other settings. Eisner found that "Only a minority of subjects who lived with a smoker reported any domestic exposure during the previous 7 days (6 out of 17, 35%)". In contrast to those findings, Eisner found that all subjects with workplace exposure reported recent exposure at work. Janson et al. (2001) provide an example of how results may be affected by the resulting misclassification. The authors note a non-significant elevation of risk of asthma for any workplace or home ETS exposure. Examined individually, workplace exposure was associated with a higher statistically significant risk and home exposure with no apparent risk. In this case, home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. These findings indicate that as a historical marker of exposure, questions regarding exposure to ETS at work may be more important than simple spousal smoking determination. In the Reynolds "teacher's cohort", they have noted that beginning in the 1980s workplace exposure had become the primary exposure source.

In the questionnaire for women in the American Cancer Society Cancer Prevention Study 2 upon which the Wartenberg et al. (2000) cohort study was based, the question upon which exposure to environmental tobacco smoke was determined was as follows:

Whether or not you smoke, on the average, how many hours a day are you exposed to cigarette smoke of others: At home___ At work___ In other areas___.

Depending on when in your life you are asked this question, the answer could vary widely, and so therefore does the exposure assignment. This points out the importance of adequate exposure history in determining classification. Given this example, one can understand why one might see different results from studies that include fuller, lifetime exposure histories than from those studies that ascertain exposure only at a single point in time or a single exposure location.

Comment 14:

e. The Cal/EPA report cites at least ten studies that have evaluated the association of breast cancer with active or passive smoking in relation to specific genetic polymorphisms (Ambrosone 1996, Millikan 1998, Morabia 2000, Chang-Claude 2002, Zheng 1999, Gammon 1999, Conway 2002, Brunet 1998, Ishibe 1998, Zheng 2002). All of these studies have limited statistical power to assess gene-environment interactions, and report conflicting findings (Figures 4a-4d). For example, Ambrosone 1996 found increased risk

of post-menopausal breast cancer associated with active smoking only among women with slow acetylator NAT2 genotype. This conflicts with the findings of Morabia 1998, which showed increased risk in both slow and rapid acetylators and with the results of Millikan 1998, who found no association for either genotype. Even more limited are studies regarding polymorphisms in NATI (Zheng 1999), p53 (Gammon 1999), or BRCAI and BRCA2 (Brunet 1998). While it is legitimate to hypothesize that genetic susceptibility may modify the relationship between tobacco smoke and breast cancer (pgs 7-132 & 7-133), the hypothesis is not currently supported by studies of this issue. The inclusion of Figure 7.4.3 (page 7-138) suggests that that the results currently available on genetic susceptibility provide reasonable support for a causal relationship between ETS and breast cancer. Since this is not the case, we suggest that Figure 7.4.3 be dropped unless it is used to illustrate the inconclusiveness of currently available data.

Response:

Figure 7.4.3 was inserted to illustrate another point made in the text. Unfortunately, that point was missed when one only considered the figure itself and thus was confusing to several commenters. We appreciate Dr. Thun's suggestion and figure 7.4.3 has been removed. While we agree that any genetic susceptibility modifying the relationship between tobacco smoke and breast cancer has yet to be firmly established, the majority of studies now find either statistically non-significant or significant interactions between human genetic characteristics, smoking, and breast cancer incidence. The level of statistical significance is a function of the size of these studies which have been limited by financial and other considerations. Additionally, accounting for the full spectrum of interactions necessary to fully explore possible risk is difficult as there may be interactions between age at exposure, age at first pregnancy, intensity and duration of exposure, genetic phenotype, etc. A meta-analysis of the various studies is not feasible since there are few studies which have measured outcomes for the same variables. Below is a chart of recent studies exploring genetic polymorphisms and susceptibility to breast cancer among active smokers which we have added to the active smoking section of the document. As noted in the chart, there are some studies which indicate strong effects of metabolic enzyme profiles, although others may not. Looking at a single enzyme does not give the complete picture because there are many different carcinogens in tobacco smoke metabolized by several different enzymes (both Phase I and Phase II). Thus the resulting net effect for a given individual depends on the entirety of the metabolic enzyme profile as far as dose of ultimate carcinogen is concerned. In addition, Couch et al. (2001) found that those smokers with high familial rates of breast and ovarian cancer have high elevated risk of breast cancer compared to nonsmokers. The point we are making is that genetics plays a role in chemical carcinogenesis and there appears to be susceptible subpopulations for carcinogenicity of tobacco smoke.

Gene Polymorphisms and Genetic Susceptibility to Breast Cancer Among Active Smokers

Study	Polymorphism	Target group	Comparison group	OR (95% CI)
Millikan		**Quit smoke ≤ 3 yr**	Never smoker with or	
et al., 1998	NAT2[1] fast	Postmenopausal	without ETS exposure	7.4 (1.6; 32.6)
		Premenopausal		1.5 (0.6; 4.0)
	NAT2 slow	Postmenopausal	"	2.8 (0.4; 8.0)
		Premenopausal	"	1.9 (0.5; 7.9)
			"	
		Current smokers		
	NAT2[1] fast	Postmenopausal		1.4 (0.7; 2.8)
		Premenopausal	"	1.1 (0.5; 2.3)
	NAT2 slow	Postmenopausal	"	1.1 (0.6; 2.2)
		Premenopausal	"	0.8 (0.4; 1.6)
			"	
Morabia	NAT2 fast	Postmenopausal	Never-smoker, no ETS	8.2 (1.4; 46.0)
et al., 2000	NAT2 slow	"	ETS only	2.5 (1.0; 6.2)
	Fast & slow	Premenopausal	Never-smoker, no ETS	2.9 (1.1; 7.5)
Delfino	NAT2	Postmenopausal	Low risk controls	1.29 (0.74 ; 2.27)
et al., 2000		Premenopausal		1.15 (0.49 ; 2.79)
		All ages		1.25 (0.27; 5.82)
Krajinovic	NAT2 fast	BC[2] smokers	BC nonsmokers	2.6 (1.1; 6.3)
et al., 2001		(pre-& post)		
Chang-	NAT2 fast	Pre- and post-	Never-smoker, no ETS	1.22 (0.59; 2.54)
Claude	NAT2 slow	menopausal	"	1.67 (0.67; 2.89)
et al., 2002				
Zheng		Smoke start <18		
et al., 2002	GSTT1[3] null	Postmenopausal	Never-smokers	2.9 (1.0; 8.8)
	GSTT1 positive			1.1 (0.6; 1.9)
	GSTT1 null	Pre- and post-	Never-smokers	1.7 (0.8; 3.7)
	GSTT1 positive	Menopausal		1.0 (0.7; 1.6)
		Current smokers		
	GSTT1[3] null	Postmenopausal	Never-smokers	2.3 (0.6; 8.9)
	GSTT1 positive			1.1 (0.6; 2.1)
	GSTT1 null	Pre- and post-	Never-smokers	1.1 (0.4; 2.7)
	GSTT1 positive	Menopausal		1.1 (0.6; 1.9)
Saintot	Val CYP1B1[4]	Pre- and post-	Leu/Leu nonexposed	2.32 (1.00; 5.38)
et al., 2003	His SULT1A1[5]	menopausal	Arg/Arg nonexposed	2.55 (1.21; 5.36)
	Met COMT[6]		Val/Val nonexposed	1.42 (0.65; 3.13)
Couch	High familial	1st degree relative	Never-smokers	1.8 (1.2; 2.7)
et al., 2001	BC risk	2nd degree	"	1.1 (0.8; 1.5)
		Married in	"	1.2 (0.9; 1.6)
	Highest risk (5+	Sisters and daughters		
	family members	SMR	"	5.8 (1.4-23.9)
	affected)[7]			2.3 (0.9-6.0)

[1]NAT2 = N-acetyltransferase; [2]BC = breast cancer; [3]GSTT1 = Glutathione S transferase T1 [4]CYP1B1 = Cytochrome P-450 1B1; [5]SULT1A1 = Phenol-sulphotransferase 1A1; [6]Catechol-O-methyltransferase; [7]Highest risk families were defined two ways: those with five or more members with either ovarian of breast cancer or those with two or more observed cancers than expected. From the latter definition was derived the number based on the SMR.

Comment 15:

f. Studies of the timing of tobacco smoke exposure in relation to breast cancer risk are similarly inconsistent (Figure 5). Two studies (Morabia 1996 & Lash 1999) report an equivalent increase in risk associated with active smoking whether smoking began before or after the first pregnancy; Band 2002 reports an association with premenopausal breast cancer only when active smoking occurs before the first pregnancy; Kropp 2002 and Egan 2002 report no significant difference related to the timing of exposure. Reynolds 2004 reports some increase in the risk of postmenopausal breast cancer in women who smoked at least five years before first pregnancy.

Response:

While there is not total uniformity described by your figure 5, the figure does reflect an increase in risk measured in at least some portion of the metrics of five of six of the studies presented in the "exposure prior to first pregnancy" portion. Some inconsistencies in what has been observed with regards to timing and risk may be the result of random variation related to relatively small numbers in the critical exposure groups. It should be noted that the OR plotted for Egan (2002) is not significant but that they report, for smokers who started before age 16, an OR of 1.31 (CI 1.07-1.61). Johnson (not included in your figure 5) reports for premenopausal breast cancer and starting smoking before age 15 an OR of 2.1 (CI 1.0-4.3). A number of studies have demonstrated elevated risk resulting from exposure during a period of breast development at least for some metrics. An exact understanding of the dynamics of the critical exposures has not been established and existing measures may be sub-optimal for consistently teasing out the risk, because it appears to be more complex than a straight dose-response relationship.

Comment 16:

g. The data in figures 2-4 are equally inconsistent with regard to risk of pre versus post-menopausal breast cancer in studies of active smoking or ETS exposure. The currently available data do not convincingly demonstrate a stronger association of ETS with any particular type of breast cancer, nor do they establish that past studies underestimated the association by studying the wrong endpoint.

Response:

Please refer to the response to comment 8.

Specific comments:

Comment 17:

Page 7-79 through 7-81: It is important not to confuse studies of nasopharyngeal cancer with those pertaining to nasal sinus cancer. Both are extremely rare in the United States, but nasopharyngeal cancer is not rare in certain Asian and native-Alaskan populations. The only

studies cited that pertain to nasal sinus cancers were those reviewed in the 1997 Cal/EPA report. All of the newer studies pertain to nasopharyngeal cancer.

Response:

The comment is correct and the text will be changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. It is of interest to note that in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002) report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS also would have similar effects in both sites.

As mentioned in our response to comments by M. LeVois, 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 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, but 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 suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Comment 18:

IARC reviewed the studies of active and passive smoking in relation to cancers of the nasopharynx, nasal cavity, and paranasal sinuses. IARC concluded that active smoking was causally related to cancers of the nasal cavity and paranasal sinuses, but that the evidence regarding ETS exposure was "conflicting and sparse". It was considered implausible that the association seen with ETS in these studies was stronger than that seen with active smoking.

Response:

With respect to active smoking and nasopharyngeal cancer, IARC reported:

> "An increased risk for nasopharyngeal cancer among cigarette smokers was reported in one cohort study and nine case–control studies. Increased relative risks were reported in both high- and low-risk geographical regions for nasopharyngeal cancer. A dose–response relationship was detected with either duration or amount of smoking. A reduction in risk after quitting was also detected. The potential confounding effect of infection with Epstein–Barr virus was not controlled for in these studies; however, such an effect was not considered to be plausible. No important role was shown for other potential confounders."

In reporting that an association between ETS and nasopharyngeal cancer is unlikely to be stronger than that seen with active smoking, IARC has not ruled out an ETS effect. A plausible explanation for the apparently disparate effects of ETS versus active smoking may lie in the window of exposure mentioned above. In those studies, childhood exposures to ETS were associated with a greater risk of nasopharyngeal cancer while adult exposures were not. In addition, as implied in IARC's statement, nasopharyngeal cancer is strongly associated with infection by Epstein-Barr virus (EBV). In vitro, B lymphocytes infected with lytic EBV were found to be susceptible to chemical induction by extracts of smokeless tobacco in terms of decreased cell population growth, and increased cell death and apoptosis (Jenson et al., 1999). Although it is not clear whether there is an interaction between tobacco smoke and EBV in the induction of at least some nasopharyngeal or sinus cancers, it is certainly plausible.

Comment 19:

1) Page 7-92, Active Smoking, line 6: The Wartenberg et al. 2000 study considered only second-hand smoke and should not be listed here. The correct reference is Cable et al., 1994 (S), who studied active smoking in relation to fatal breast cancer in the ACS cohort. The study by Terry et al. 2002 should be cited here rather than on page 7-122 (2"d last line) because it concerns active smoking.

Response:

Thank you for pointing out these inconsistancies. The revised document will show these corrections.

Comment 20:

2) Page 7-134, 2nd full pp, 1st sentence: While it is true that there is concordance between animal and human susceptibility to carcinogenesis from a particular exposure, there is much less concordance with the affected site.

Response:

OEHHA agrees that this is generally the case, and in fact goes on to argue later in the same paragraph that this <u>may</u> result in an underestimate of the number of potential human mammary carcinogens in tobacco smoke, since a case can be made (based on background rates of incidence) that human mammary tissue is a relatively sensitive site compared to some rodent models where other sites (e.g. liver, lung) have very high background rates and/or apparent sensitivity to chemical carcinogens.

Comment 21:

3) Page 7-134, last pp: The report should acknowledge that animal models of mammary cancer are less predictive of human breast cancer than are animal models of certain other cancer sites.

Response:

OEHHA does not agree with this assertion in the general form stated. Since the comment does not specify which other sites are to be referred to for comparison, a detailed response is difficult. There is also a concern that this comment may represent a prejudgment of the issue, since apart from tobacco- and alcohol-related effects most of the human evidence on induction of breast cancer by extrinsic chemical agents is based on prevalence or "ecological" studies that are notoriously hard to evaluate. Most of the clear-cut comparisons between animal and human cancer responses depend for the human evidence on occupational cohorts and case groups, in which women are notoriously under-represented.

Comment 22:

4) Page 7-136, 1st pp, 1st sentence: While the sentence is technically true, three of the studies cited (Santella 2000, Rundle 2000, and Li 2002) mention finding no association between smoking status and the formation of DNA adducts or oncogene formation in breast tissue.

Response:

As noted in the comment, OEHHA avoided claiming that any such association was either expected or found; the point is that mammary tissue is susceptible to the same sort of genetic alterations, in response to polycyclic aromatic hydrocarbon exposures, that are known precursors of tumor appearance in other tissues. Given the difficulties in establishing the degree of tobacco smoke exposure from measures of smoking status detailed in the document; it is unremarkable that some of these studies failed to demonstrate this latter association. In addition to the sources cited in the draft report, the following should also be considered:

Firozi et al (2002) and a previous paper by Li et al. (1996) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted in smokers but not in non-smokers. Gene-gene interaction was also noted in smokers with certain CYP1A1 and GSTM1 null polymorphisms combined having much higher levels of DNA adducts than either individually. Their findings suggest that polymorphisms of CYP1A1, GSTM1, and NAT2 significantly affect either the frequency or the level of DNA adducts in normal breast tissues of women with breast cancer, especially in smokers.

Similarly, Faraglia et al. (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend ($P = 0.04$) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status ($P = 0.03$). An increase in adduct levels with passive smoking status alone (never, former,

current) was seen but the trend was not statistically significant: a significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking.

Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003). Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke.
Carcinogenesis **24**(4):719-25.

The revised report will include these two important references.

Comment 23:

5) Page 7-136, 1st pp, last sentence: Whyatt et al. 1998a measured DNA adducts in placental tissue; Anderson et al. 2001 measured urinary excretion of nicotine metabolites. These studies do not directly involve breast tissue.

Response:

OEHHA did not intend to imply that they did so, but used these examples to demonstrate that humans exposed to ETS are subject to internal (metabolic) exposures characteristic of polycyclic aromatic hydrocarbons and similar compounds that have been identified as components of ETS. Clarification of this will be added to the document along with the information on DNA-adducts presented in above response to comment 5.

Comment 24:

6) Page 7-136, 2" pp: None of the studies cited above document DNA adducts or mutations in breast tissue due to ETS.

Response:

See above responses to comments 5 and 6.

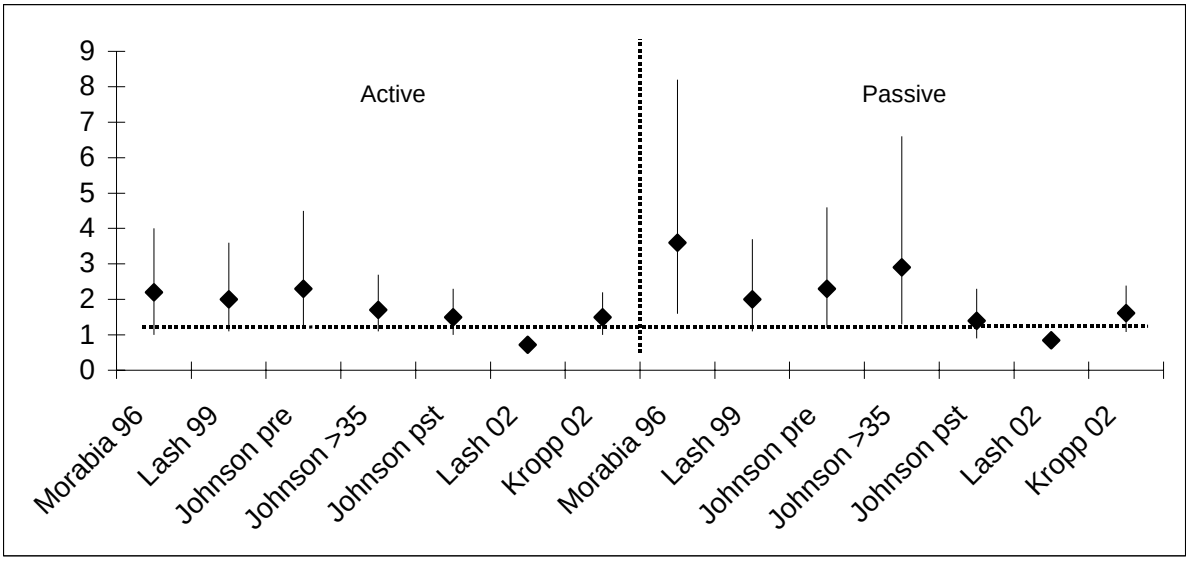
Comment 25:

7) Page 7-137, Figure 7.4.2: The horizontal dotted line should represent a RR of 1.0 on the Y axis, not be below it. If this line is repositioned the results by Lash 2002 will be below the line. The selection of studies included in this graph is puzzling. The subgroup findings from Johnson for women > 35 years should not be included, whereas the results from Morabia 1996, ChangClaude 2002, Egan 2002, and Reynolds 2004 should be added.

Response:

The dotted line location is an artifact of the word processing program and we will correct that. Morabiaet al. (1996) has been added per your suggestion. Chang Claude 2002 is not considered separately since it utilizes the participants of the same study as Kropp and Chang-Claude (2002) which is included. Reynolds et al.(2004) and Egan et al. (2002) are not included since they were not considered to be examples of studies that had complete measures of lifetime exposure to ETS in various settings.

Figure 7.4.2. Recent studies of breast cancer risk utilizing an unexposed referent group



Comment 26:

8) Page 7-138, top pp: The issue of the "consistency" of results from the case-control studies only becomes important if one has satisfied considerations of validity.

9) Page 7-13, top pp & Figure 7.4.3: See general comment 3c above.

Response:

The issues regarding validity of the case-control studies are addressed in several of the other responses to Dr. Thun's comments including comments 11, 12, and 13.

Comment 27:

10) Page 7-144, Figure 7.4.4: The scale on the Y-axis should consistently be either arithmetic or log transformed but not both. Use of the log-transformed scale may obscure the degree of variability across studies and the implausibly large RR estimates in some studies. Hirayama 1984 or Sandler 1985 should presumably not be included in the Figure, since

their published analyses were incomplete and did not control for the established risk factors for breast cancer.

Response:

We have in general used a log transformed scale for the figures. The log scale is preferable for RRs because it more accurately reflects the magnitude of the effect. E.g., on the log scale, the physical distance between 0.5 and 1 is the same as between 1.0 and 2.0 and between 2.0 and 4.0 (all reflect a 2x difference in relative risk). In some instances it was felt to be visually more appropriate to present the data in an arithmatic form. When clarity demanded consideration of alternative formatting we allowed for what we felt was the most clear presentation. Each study presents strengths and weaknesses that need evaluation.

In our evaluation Hirayama and Sandler were of adequate quality to consider in the more complete analysis of the data. You can see that they are given an open diamond which while signifying having missed likely sources of exposure allows you to see in the summary statistic "with important ETS sources included" that removing these studies in fact results in a stronger association with breast cancer. The analysis was robust to inclusion or exclusion of various studies.

Comment 28:

11) Page 7-146, Figure 7.4.5: Several studies included in this figure do not control for important covariates such as age at first birth and/or alcohol consumption (Hirayama 1984, Sandler 1985, Smith 1994, Millikan 1998, Delfino 2000).

Response:

All of the studies mentioned above in #11 except Smith are considered in our analysis as lower quality studies and are designated with an open diamond. While it is true that the primary consideration for open diamond was based on the completeness of the exposure history, you can conveniently observe the effect of dropping these studies on the summary statistic by looking at the RR-important ETS sources collected. Smith we believe correctly belongs in the grouping of more complete studies. Their data on passive smokers included adjustments for age, age at menarche, age at first full term pregnancy, breastfeeding, total oral contraceptive use, family history, and alcohol consumption at age 18 years. This study only considered subjects under 36 years of age and therefore consumption at 18 (the time of highest quantity of consumption) was considered a reasonable measure. Though there was some difference in alcohol consumption at ages 18, 25, and at diagnosis, various analyses were performed for each age and none found statistically significant change in the impact on breast cancer.

References cited in Comments

1. California Environmental Protection Agency. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Part B: Health Effects. Sacramento, CA:

California Environmental Protection Agency, Office of Environmental Health Hazard Assesment; 2003.

2. California Environmental Protection Agency. Health Effects of Exposure to Environmental Tobacco Smoke: Final Report. Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assesment; 1997.

3. IARC. Tobacco Smoke and Involuntary Smoking. Vol 83. http://193.52.164.11/htdocs/monographs/vol83/02-involuntary.html ed. Lyon: International Agency for Research on Cancer; 2004.

4. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. British J Cancer 2002;87:1234-45.

5. Calle E, Miracle-McMahill H, Thun M, Heath CJ. Cigarette smoking and risk of fatal breast cancer. Am J Epidemiol 1994;139:1001-7.

References cited in responses

Armstrong R, Imrey P, Lye M, Armstrong M, Yu M, Sani S (2000). Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Intl J Epidemiol 29:991-8.

Band PR, Le ND, Fang R, Deschamps M (2002). Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. Lancet 360(9339):1044-9.

Chang-Claude J, Kropp S, Jager B, Bartsch H, Risch A (2002). Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 11(8):698-704.

Collaborative Group on Hormonal Factors in Breast Cancer (2002). Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 87(11):1234-45.

Couch FJ, Cerhan JR, Vierkant RA, Grabrick DM, Therneau TM, Pankratz VS, Hartmann LC, Olson JE, Vachon C M, Sellers TA (2001). Cigarette smoking increases risk for breast cancer in high-risk breast cancer families. Cancer Epidemiol Biomarkers Prev. 10(4):327-32.

Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao S, Gim JS-y, Ma HL, Butler J, Anton-Culver H (2000). Breast cancer, passive and active cigarette smoking and N-acetyltransferase 2 genotype. Pharmacogenetics 10(5):461-9.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD (2001). Measurement of environmental tobacco smoke exposure among adults with asthma. Environ Health Perspect. 2001 Aug;109(8):809-14.

Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA (2002). Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. Epidemiology 13(2):138-45.

Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003). Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke. Carcinogenesis 24(4):719-25.

Firozi PF, Bondy ML, Sahin AA, Chang P, Lukmanji F, Singletary ES, Hassan MM, Li D (2002). Aromatic DNA adducts and polymorphisms of CYP1A1, NAT2, and GSTM1 in breast cancer. Carcinogenesis 23(2):301-6.

Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. (1994). Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA 271(22):1752-9.

Fontham ET, Correa P, Wu-Williams A, Reynolds P, Greenberg RS, Buffler PA, Chen VW, Boyd P, Alterman T, Austin DF (1991). Lung cancer in nonsmoking women: a multicenter case-control study. Cancer Epidemiol Biomarkers Prev 1(1):35-43.

Hertz-Picciotto (1998). Environmental epidemiology. In:Modern Epismiology. Rothman K and Greenland S, eds. Lippincott-Raven Publishers, Philadelphia, PA. Pp 557-561.

Hirayama T (1984). Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13(6):680-90.

Horn-Ross PL, Hoggatt KJ, West DW, Krone MR, Stewart SL, Anton H, Bernstei CL,Deapen D, Peel D, Pinder R, Reynolds P, Ross RK, Wright W, Ziogas A. Recent diet and breast cancer risk: the California Teachers Study (USA). Cancer Causes Control. 2002 Jun;13(5):407-15.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358(9299):2103-9.

Jee SH, Ohrr H, Kim IS (1999). Effects of husbands' smoking on the incidence of lung cancer in Korean women. Intl J Epidemiol 28(5):824-8.

Jenson HB, Baillargeon J, Heard P, Moyer MP (1999) Effects of smokeless tobacco and tumor promoters on cell population growth and apoptosis of B lymphocytes infected with Epstein-Barr virus types 1 and 2. Toxicol Appl Pharmacol. 1999 Oct 15;160(2):171-82.

Johnson KC, Hu J, Mao Y (2000). Passive and active smoking and breast cancer risk in Canada, 1994-97. The Canadian Cancer Registries Epidemiology Research Group. Cancer Causes Cont 11(3):211-21.

Krajinovic M, Ghadirian P, Richer C, Sinnett H, Gandini S, Perret C, Lacroix A, Labuda D, Sinnett D (2001). Genetic susceptibility to breast cancer in French-Canadians: role of carcinogen-metabolizing enzymes and gene-environment interactions. Intl J Cancer 92(2):220-25.

Kropp S, Chang-Claude J (2002). Active and passive smoking and risk of breast cancer by age 50 years among German women. Am J Epidemiol 156(7):616-26.

Lash TL, Aschengrau A (1999). Active and passive cigarette smoking and the occurrence of breast cancer. Am J Epidemiol 149(1):5-12.

Lash TL, Aschengrau A (2002). A null association between active or passive cigarette smoking and breast cancer risk. Breast Cancer Res Treat 75(2):181-4.

Li D, Wang M, Dhingra K, Hittleman WN. (1996). Aromatic DNA adducts in adjacent tissues of breast cancer patients, clues to breast cancer etiology. Cancer Res., 56:287-293.

Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD, Qaqish B (2000). The association of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). Cancer Causes Cont 11(3):271-78.

Millikan RC, Pittman GS, Newman B, Tse CJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA (1998). Cigarette smoking, N-acetyltransferase 1 and 2, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 7(5):371-78.

Morabia A, Bernstein M, Heritier S, Khatchatrian N (1996). Relation of breast cancer with passive and active exposure to tobacco smoke. Am J Epidemiol 143(9):918-28.

Morabia A, Bernstein MS, Bouchardy I, Morris MA (2000). Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. Am J Epidemiol 152(3):226-32.

Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S (2001). Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Cont 12(9):797-802.

Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A (2004). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. J Natl Cancer Inst. 96(1):29-37.

Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985). Cancer risk in adulthood from early life exposure to parents' smoking. Am J Public Health 75(5):487-92.

Shrubsole MJ, Gao YT, Dai Q, Shu XO, Ruan ZX, Jin F, Zheng W (2004). Passive smoking and breast cancer risk among non-smoking Chinese women. Int J Cancer 110(4):605-9.

Smith SJ, Deacon JM, Chilvers CE (1994). Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. UK National Case-Control Study Group. Br J Cancer 70(1):112-9.

van Belle G., 2002, Statistical Rules of Thumb. Pp 39-40. New York, NY: John Wiley

Vineis P, Bartsch H, Caporaso N, Harrington AM, Kadlubar FF, Landi MT, Malaveille C, Shields PG, Skipper P, Talaska G, Tannenbaum SR. (1994). Genetically based N-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. Nature 369(6476):154-6.

Wartenberg D, Calle EE, Thun MJ, Heath CW, Lally C, Woodruff T (2000). Passive smoking exposure and female breast cancer mortality. J Natl Cancer Inst 92(20):1666-73.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ. Jul 24;329(7459):200-5.

Yuan J-M, Wang W-L, Xiang Y-B, Gao Y-T, Ross RK, Yu MC (2000). Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. Intl J Cancer 85:364-9.

Zhang B, Ferrence R, Cohen J, Ashley MJ, Bondy S, Rehm J, Jain M, Miller A, Rohan T (2004) published as an abstract in the abstracts of the 37th annual meeting of the Society for Epidemiologic Research (June, 2004). http://www.epiresearch.org/meeting/abstractbook.pdf

Zheng T, Holford TR, Zahm SH, Owens, PH, Boyle P, Zhang Y, Wise JP Sr., Stephenson LP, Ali-Osman F (2002). Cigarette smoking, glutathione-s-transferase M1 and t1 genetic polymorphisms, and breast cancer risk (United States). Cancer Causes Control 13(7):637-45.

Zhao Y, Shi Z, Liu L (1999) [Matched case-control study for detecting risk factors of breast cancer in women living in Chengdu]. Zhonghua Liu Xing Bing Xue Za Zhi. 20(2):91-4.

Zhu K, Levine RS, Brann EA, Hall HI, Caplan LS, Gnepp DR (2002). Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Cancer. 99(1):119-23.

Comments of A. Judson Wells, PhD., Kennett Square, PA

Executive Summary

Comment 1:

Table ES.2 on page ES-11 should include incident cases of breast cancer. The number of cases for breast cancer can be estimated by using the combined odds ratios from the two best breast cancer studies (Morabia, et al., 1996, and Johnson , et al., 2000). Their combined OR is 1.67 (95% CI, 1.29-2.16). Alternatively, one could combine the ORs from the four best studies by adding Smith, et al., 1994 and Kropp, et al., 2002. This results in an OR of 1.68 (95% CI, 1.36-2.08). However, the latter result is more heavily weighted toward younger women.

Response:

Comment noted. We are concerned that it may be quite difficult to estimate attributable risk given the number of known risk factors for breast cancer that contribute to the high rate of this disease including age at menarche, age at menopause, age at first birth, parity, and whether the woman breast fed her babies. Although perhaps a relatively crude attributable risk could be developed, we felt it was best to avoid the calculation until we have a better way to account for these other known risk factors.

Comment 2:

I find the range for excess lung cancer deaths from ETS in Table ES.2, 411-1,514 for California and 7,564-26,473 for the U. S. to be higher than I thought to be reasonable. On page 7.76 in the report the range is said to be 283 to 1052 deaths for California. Assuming the population of California is about 10% of the U. S. population, this would translate to about 2,830-15,200 for the U. S. The 1992 U. S. EPA report estimated lung cancer deaths from ETS exposure for the whole country at 3,000 for never smokers plus former smokers.

Response:

We have reviewed and updated the attributable risk calculations for lung cancer utilizing the method of U.S. EPA from the 1992 report. This now replaces the previous calculation and is presented in detail in the revised document.

Comment 3:

I also wondered if there is any way to include all causes of death from exposure to ETS, either here or in Part B. There are all cause data in Gillis et al, Eur J Respir Dis 1984;65 (suppl 133):121-126 on males, 1.04 (95% CI, 0.69-1.57), and females, 1.33 (95% CI, 0.94-1.89), in western Scotland. In the extensive data that Hirayama sent me in 1988 (referred to in the breast cancer section in B) there are also all cause data for women in Japan. The age adjusted RR is 1.17 (95% CI, 1.11-1.24). There may be other sources of all cause data. I just haven't looked. It

also might be an occasion to honor G. S. Miller who is the pioneer in investigating deaths from passive smoking. In the Journal of Breathing, 1978;41:5-8, he reported that nonsmoking wives in Erie County, Pennsylvania, who were married to nonsmokers lived 4 years longer (78.8 versus 74.7) than wives married to smokers. This was 2+ years before the 1981 reports of Hirayama and Trichopoulos on ETS and lung cancer.

Response:

The current update of the OEHHA document (CAL/EPA, 1997) did not in general include additional consideration of studies that were published during the time period reviewed previously (prior to 1996). Additionally, we have decided not to include a category of "all causes of death" as it is felt to be too broad a definition to be helpful in our current review of the scientific literature.

Part A

Comment 4:

Pages III-4 and 5. There has been too little attention paid in the U. S. to the work of Pritchard et al, Environ Technol Lett 1988;9:545-552, at Harwell in England on what happens to aged, diluted ETS. They labeled tobacco smoke with a radioactive isotope of iodine in 1-iodohexadecane, which boils at 380 degrees C., about in the middle of the boiling point of tobacco tar. They used a 14.4 m3 chamber and found that, during aging and dilution, 70% of the particulate ETS tar evaporates into the vapor phase. Vapor phase tar, like other organic vapors (Bond et al, Toxicol Appl Pharmacol 1985;78:259-267) would deposit quantitatively in the lung, and the lung has no clearance mechanism for vapor phase deposits, whereas only about 15% of the particulates deposit in the lung, the remainder being exhaled. This phenomenon could go a long way toward explaining why the passive risk is so similar to the active risk in non-contact sites like the heart and breast. It appears that the tar compounds that would evaporate would have molecular weights in the 100 to 200 range which would include quinoline, ethyl quinoline, benzoquinoline, phenanthridene, nornicotine, beta-naphthyl amine, nitroso pyrolidine, nitroso nornicotine, pyrene, fluoranthene, phenol, the cresols, 2,4-dimethyl phenol, catechol, and the methyl catechols, all of which have some carcinogenic activity.

Response:

ARB staff have responded to this comment in their summary of the comments on Part A.

Part B

Comment 5:

On page 4-6 in the discussion of McMartin et al., 2002 there is no mention of the significance of higher nicotine in the SIDS babies, but not higher cotinine. This means that the relevant exposure occurred during a very short time before the death occurred, namely, during the half-life of nicotine.

Response:

Thank you for pointing out this important fact. The review has been edited to mention this.

Comment 6:

In Chapter 6 there is no mention of Chronic Obstructive Lung Disease (COLD) as an outcome of ETS exposure. I know of two such reports. Kalandidi et al. Lancet, 1987;Dec 5:1325-26, found that never smoking wives married to smokers had incidence ORs of 1.3 (95% CI, 0.7-2.3) with exposure to less than 300,000 husband's cigarettes in their lifetime, and 1.7 (95% CI, 0.8-3.4) for exposure to more than 300,000 cigarettes, versus wives married to nonsmokers. Hirayama, in the 1988 personal communication referred to above, found an age adjusted RR of 1.32 (95% CI, 0.8-2.1) for death from emphysema or bronchitis when his Japanese wives were married to a smoker vs. a nonsmoker. There may be other references, but I haven't looked.

Response:

The purpose of the current document is to examine more recently published findings, which may extend or modify conclusions reached in the 1997 document. Unless it has been considered essential to our findings we have not included reviews of work prior to 1997.

Comments on Chapter 7 (Cancer):

(General & all cancers)

Comment 7:

In Chapter 7, Table 7.0B there is no mention of radioactive polonium which I remember as a component of ETS, and which I believe is carcinogenic.

Response:

OEHHA thanks the commenter for pointing out this omission. IARC Monographs Vol 78 (2001) identified all internally deposited α-emitting radionuclides as carcinogenic to humans (Group I), and also found sufficient evidence of carcinogenicity in animals specifically for polonium-210 (lung cancer in hamsters). 210Po is responsible for over 99% of the α-activity in tobacco smoke (IARC, 2001, citing Cohen et al., 1980). Table 7.0B will be amended by the following addition to reflect these data:

^{210}Polonium (0.04-0.1 μCi) (7)	Sufficient	Sufficient	Vol. 78, pp. 465-477. (Group 1 listing is of all internally deposited α-emitting radionuclides, considered as a group).

7. US EPA (1992)

Comment 8:

On page 7-10 the reference to the EPA report as Wells (1992) could be more specific by listing it as (Wells, 1992b) and referencing it as Wells AJ (1992b), In: U.S. EPA (1992) Respiratory Health .....Washington, DC., Appendix B. Reference1992a should be reserved for my 1992 letter in Am J Epidemiol, which goes with the 1991 letter in AJE.

Response:

The citation has been clarified in the text and table of references as suggested.

Comment 9:

You will probably be criticized if you don't refer to the work of tobacco consultant Peter Lee, who still doesn't agree that misclassification of smokers as nonsmokers is a small effect.

Response:

OEHHA has separately received a number of comments from Mr. Lee, and will be responding to these both directly and, where appropriate, by additions to the document text.

Comment 10:

On page 7-12 the 1997 report missed the all cancer passive smoking data in Gillis et al., Eur J Respir Dis 1984;65 (suppl 133):121-126. They report on 44 male cancer deaths and 144 female cancer deaths. In my 1988 paper in Environment International, Wells AJ (1988), Environ Int 1988;14:249-265, the risks from cancers other than lung (five studies) and lung cancer are reported separately, but they are easily combined to get total cancer results. My paper in J Women's Cancer 2000;2(2):55-66, Table 1, also gives a total cancer risk of 1.4 (95% CI, 1.1-1.8) by combining the results from various studies.

Response:

The current update of the OEHHA document (CAL/EPA, 1997) did not in general include additional consideration of studies that were published during the time period reviewed previously (prior to 1996). In addition, we feel that while the findings are interesting, that there is little added to our review by combining data in a meta-analysis over such a broad category of outcomes as total cancer risk.

Comments on Lung cancer:

Comment 11:

On page 7-67 mention should be made about the errors in underlying studies of lung cancer from workplace ETS exposure, specifically Wells AJ et al., J Natl Cancer Inst 1997;89:821-822 on errors in Garfinkel et al (1985), and Wells (1998b) on errors in Janerich, et al., (1990).

Response:

Both the specific studies criticized were described in the 1997 document: it is not clear that they deserve further individual consideration in this update. The current document refers to the more general considerations by citing OEHHA (1997) and Wells (1998b). This reference has been expanded by including the sentence:

"Some of the earlier non-positive meta-analyses were affected by exposure estimation inconsistencies and errors in reporting of the underlying studies, or inappropriate weighting factors applied in the meta-analyses, as described in detail by Wells and Henley (1997) and Wells (1998b)."

Comment 12:

On page 7-74 the meta-analysis in Wells 1998b of 15 studies, RR = 1.19 (95% CI, 1.07-1.34), should be added to the list in the first paragraph even though it covers only workplace exposure.

Response:

The citation has been added, with the list re-ordered by date.

Comments on Breast cancer:

Comment 13:

On page 7-93 the statement that Millikan's ORs for current smoking are versus never active/passive of 1.0 (0.7-1.4) and following is wrong. Those ORs in their Table 2 are versus all never smokers, except for the ETS result at the bottom of the table. At the top of page 7-94 the "limitations" should include not using non-ETS exposed never smokers in the referent for the main OR's as well as the age 18+ referent for the passive smoking OR.

Response:

The passage has been modified as follows:

No association was observed between breast cancer and current active smoking versus never smokers in all women [adjusted OR 1.0 (95% CI 0.7-1.4)] in premenopausal women [adjusted OR 0.9 (95% CI 0.5-1.5)], or in postmenopausal women [adjusted OR 1.2 (95% CI 0.7-2.0)] (see Table 7.4A). The authors note that "when we excluded women with exposure to ETS from the referent group, ORs for active smoking were unchanged or slightly attenuated."

Comment 14:

On page 7-97, Marcus et al., I would add "all" to the last word in line 6. Also it should be noted that the ETS results in their Table 2 are for smokers as well as nonsmokers.

Response:

All has been inserted as suggested. The data presented in this section is from their table 3.

Comment 15:

On page 7-101 there is a reference to Wells, 2002 (should be 2003), but this reference does not appear in the reference list on page 7-203. The reference is Wells AJ. Breast cancer and tobacco smoke [letter]. Br J Cancer 2003;89:955.

Response:

The correction has been made in the document.

Comment 16:

On page 7-102, last line, add "all" to never-smokers. The 1.60 RR on the next page is probably crude. The adjusted RR in Table II is 1.61 (95% CI, 1.19-2.19). It would also be worth including their RR for exposure for 40+ years and 20+ cigarettes per day of 1.83 (95% CI, 1.29-2.61).

Response:

The correction has been made in the document.

Comment 17:

On page 7-104, another weakness of the Band et al., study is that they did not consider using non-ETS exposed never-smokers as their referent.

Response:

The section has been changed as follows:

Limitations of the study include lack of consideration of time-since-first-exposure in the dose-response analysis of pack-years and lack of data concerning ETS and thus including ETS exposed in the referent population (potentially biasing results towards the null).

Comment 18:

On page 7-103 under Terry, et al., 2002a, mention should be made of their observation that 40+ cigarettes per day yields a RR of 1.34 (95% CI, 1.06-1.69) and that 40+ years and 20+ cigarettes per day yields 1.83 (95% CI, 1.29-2.61). Also Terry, et al., should be included in Table 7.4B. Mention in the active smoking section might be made of Couch, et al., Cancer Epidemiol Biomark Prev 2001;10:327-332, that women with a family history of three or more cases of breast or ovarian cancer had a breast cancer RR of 2.4 (95% CI, 1.2-5.1) for ever smokers

relative to never smokers. Also Manjer, et al., Int J Cancer 2001;91:580-584, report that women with estrogen receptor-negative breast tumors have RRs of 2.21 (95% CI, 1.23-3.96) for current smokers and 2.67 (95% CI, 1.41-5.06) for former smokers, relative to women who have never smoked. I believe there is other evidence that women with estrogen-negative tumors are at higher risk from tobacco smoke.

Response:

Thank you for pointing out the additional papers, which have been added to the review. The table has been modified to include data from Terry.

Comment 19:

In Table 7.4B there is no referent shown for Lash and Aschengrau (1999), Kropp and Chang-Claude (2002), or Lash and Aschengrau (2002). In Table 7.4C on page 7-118 there is no referent shown for Morabia et al. (2000). These should all be "No active/passive". Also I have a letter from Sarah Smith in which she says, referring to their paper, Smith et al., (1994), that ever smokers not exposed to other's ETS had an OR of 2.00 (95% CI, 0.98-4.12) compared with non-ETS exposed never smokers. This information was published in Wells (1998b).

Response:

Referents for Lash and Aschengrau (1999), Kropp and Chang-Claude (2002), Lash and Aschengrau (2002), and Morabia et al. (2000) have been added.

Comment 20:

In pages 7-119 and following the reference Wells (1998) should be changed to Wells (1998b).

Response:

The reference to Wells (1998) appears now to be correct as a result of corrections applied to the table of references (compare the responses to Comments 8 and 9).

Comment 21:

On pages 7-120 and 7-121 re the Smith et al., (1994) paper the risks shown were taken from their Table IV, which is for smokers and nonsmokers exposed to ETS. Even though there is less statistical significance in individual categories because of the smaller numbers, I think CalEPA ought to go with the numbers in Smith's Table V for the effects of ETS exposure on never smokers only. Throughout the literature the passive smoking risk that is sought is that for ETS-exposed never smokers relative to non-ETS exposed never smokers. One could set up separate studies of the effect of ETS exposure on smokers, but the two should never be combined. The high statistical significance that you show for lifetime exposure based on Table V in Smith, et al., 2.53 (95% CI, 1.19-5.36) is good enough. The whole paragraph should be rewritten.

Response:

This paragraph has been modified.

Comment 22:

On page 7-122 there is a reference to Terry et al., 2002. There are two Terry 2002 references in the reference list, page 7-202. Here you probably mean 2002b since there are no passive smoking data in 2002a. Also on page 7-122 there is no mention of Zhao et al., Matched case control study for detecting risk factors of breast cancer in women living in Chengdu (in Chinese). Chung Hua Liu Hsing Ping Hsueh Tsa Chih (Clin J Epidemiol, probably for China) 1999;20:91-94, nor of Lui et al., Passive smoking and other factors at different periods of life and breast cancer risk in Chinese women who have never smoked - a case control study in Chongqing, People's Republic of China. Asian Pacific J Cancer Prev 2000;1:131-137, both of which contain data on passive smoking and breast cancer as indicated in Table 7.4E, but there are no explanatory paragraphs for them in pages 7-123 to 7-131, nor are they included in the reference list, pp 7-198, 7-204.

Response:

The Terry et al. citation has been changed. Zhao and Liu have been added.

Comment 23: The best thing to do with Marcus et al, (2000) pages 7-126 and 127, is to omit it from the passive smoking part of the report. There are no good passive smoking data in it. All of the exposed groups include smokers as well as never smokers. See discussion above under Smith et al. In the OR where the referent is "no exposure and no history of active smoking" the smokers were eliminated in the referent, but, based on the cell counts, the smokers are still included in the exposed group.

Response:

The following qualifier has been appended to the description of the Marcus study. "However, these data are of limited usefulness in evaluation of passive smoking risk to non-smokers since, though the unexposed category is limited to never smokers, the exposed category includes both never and ever active smokers."

Comment 24:

Under Morabia, et al., (2000 and 1998) on page 7-127, would it be helpful to refer to Figure 7.4.3 toward the end of the first paragraph. Under Wartenberg, et al., (2000) at the top of page 7-129, the wording could be a little more definite. Try "Nevertheless, since the ETS exposures other than from spouse were included in the questionnaire only at one point in time, namely, at enrollment, the potential for...." Under Nishino, et al., (2001) page 7-129, mention should be made of their statement on page 801 of their paper that "women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for

breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoking exposure".

Response:

The wording has been modified as indicated in the comment.

Comment 25:

On page 7-132, under Khuder and Simon, there is an error in the paper. From their Table 2 the actual ORs for the lowest levels of exposure range from 0.80 (Wartenberg) to 3.10 (Morabia), and for highest levels, from 1.10 (Warternberg) to 3.20 (Morabia). K & S is a very sloppy paper. For example they include Marcus, et al., in the dose response list with only one value. Also the RR for Wartenberg in Table 1 is wrong.

Response:

The risk values cited have been corrected.

Comment 26:

On page 7-135, Table 7.4D, a footnote on what the IARC classifications mean would be helpful.

Response:

This information has been added to the text and to the footnotes.

Comment 27:

Also why are Delfino, et al., Egan, et al., and Wartenberg, et al., excluded from Figure 7.4.2?

Response:

The figure 7.4.2 is meant to present studies that have gathered exposure information for various sites and time periods (lifetime exposure). The above studies do not meet those criteria.

Comment 28:

On page 7-137, Nishino, et al., is also a new prospective study. Jee, et al., has dose response, 1.2, 1.3, and 1.7. Both Lui, et al., 2000 and Zhao, et al., 1999 are listed on page 7-137, but the are no descriptions of these studies in the earlier text, nor are they listed in the reference list on pages 7-198 and 7-204. Why is Millikan, et al., missing from Table 7.4E? Why is Kropp, et al., labeled "likely" in Table 7.4E and "unlikely" in Table 7.4F? Also Hirayama and Jee are "unlikely " in Table 7.4E and "likely" in Table 7.4F. On page 7-140 it is stated that there are 15 studies. Actually there are 16 studies; Millikan is missing from Table 7.4E and Lui from Table 7.4F, Figure 7.4.4 and Table 7.4G.

Response:

The indicated wording changes have been made and descriptions of the studies by Zhao and Liu added. Liu has not been added to Table 7.4F because of our concerns about some of the data that were felt to be possibly inconsistent and our inability to get those concerns clarified by the author.

Comment 29:

In Table 7.4I, page 7-149, under Delfino, et al., isn't it better to use their low risk controls (60 cases) yielding a passive OR of 1.78 (95% CI, 0.77-4.11). In Table 7.4J there is no referent shown for Lash, et al., 1999, 40/139, or for Lash, et al., 2002, 80/53.

Response:

Thank you for pointing this out, the table has been adjusted to use Delfino's low risk number which is more appropriate. Referents have been added to Table 7.4J.

Comment 30:

I find Tables 7-4I and 7.4J confusing. If Table 7.4I is supposed to include all of the case-control studies, it is missing Morabia, Smith, Liu, Sandler, Zhao, and Lash 2002. As noted above, I would omit Marcus. If Table 7.4J is supposed to include the case-control studies with dose-response, it is missing Morabia, Smith (child only, adult only, child plus adult) and Liu. On page 7-154, Table 7.4L, Hirayama and Nishino are missing. Also the word "Deaths" in the heading for Cases should be removed in both Tables 7.4L and 7.4M because some of the cohort studies used diagnosis. In Jee, the RR for wives exposed to current smokers for more than 30 years (1.7, 95% CI, 1.0-2.8) should be added to both Tables 7.4L and 7.4M.

Response:

The indicated additions and changes have been made.

Comment 31:

In the reference list on page 7-203, Wells AJ 1991, 1992a, 1998a, and 2001 should be designated as letters. Also there is an Erratum associated with 1998a, which is noted at Am J Epidemiol 1998;148(3):314.

Response:

The reference list has been modified as indicated.

Comment 32:

As a general comment on ETS and breast cancer, I know that your general plan is to discuss active smoking first, then passive smoking, and finally biological plausibility. This makes sense for lung cancer, but for breast cancer the reverse may be better. Start with the exposure windows, probable hormonal effects, and animal studies of breast specific carcinogens. Then get into passive smoking, and finally into active smoking. The advantage of this order is that it explains why the active smoking effect depends so much on the referent that is used, either including or excluding passively exposed never smokers, and it leads to an explanation of why the passive effect is almost as large as the active effect.

Response:

The revised version of the report does give greater attention to the relationship between active and passive smoking. The organization of chapters was kept as close as possible to that seen in the 1997 document so that the reader can refer to the corresponding section of that document easily.

Comments on Chapter 8

Comment 33:

In Chapter 8, Table 8.1, page 8-3, and in the text on pages 8-10 and following, the comments on Wells (1998) are restricted to workplace exposure only. Actually there is an Appendix in that paper which updates Wells' 1994 meta-analysis (J Am Coll Cardiol 1994;24:546-554). The update includes 19 studies that were available at that time, and breaks the results down by morbidity and mortality, males, females and both genders, four quality tiers, and exposure from spouse only, home only, and all adult exposures. The quality tiers were taken from my 1994 meta-analysis (above) and were based on the number and importance of the other risk factors that were adjusted for. The combined RR for morbidity for tier 1, the top quality tier, and all adult exposures for males plus females is 1.86 (95% CI, 1.20-2.88). For all home exposures only, the combined RR is 1.63 (95% CI, 1.22-2.18), and for spouse exposure only, it is 1.39 (95% CI, 1.06-1.82). This demonstrates that better questionnaires lead to higher RRs, and that the real relative risk may be nearer 1.8 than 1.25. For mortality, tier 1, males and females combined, the RR for all adult exposures is 1.87 (95% CI, 0.56-6.20), but for many fewer cases. For spouse exposure only for mortality for all studies combined, the RR is 1.21 (95% CI, 1.09-1.35), in reasonable agreement with the other meta-analyses, but less than the 1.8 from the better studies.

Response:

The table and text in chapter 8 have been modified to include the results in the appendix of that paper.

Comment 34:

On page 8-6, Table 8.1 under Raitakari, et al., it looks like ETS in the third column needs to be lowered one line. On pages 8-16/17 I could find no reference in the description of You, et al., to Figure 8.03. On pages 8-32/33/35 on platelet effects and animal studies there is no mention of the rather thorough discussions on these subjects in the 1997 report. Even with a mention of those discussions, you may want to refer to some of that work. I am thinking particularly about the work of Burghuber, et al., and Davis, et al., on platelets, Zhu, et al., on rabbits, and Penn, et al., on cockerels.

Response:

Raitakari was fixed in Table 8.1. There is a reference to Fig 8.03 in You on page 8-20. Regarding reference to works in the previous document, the following sentence appears on pg 8-36: The effect was also observed in studies by Sinzinger and Kefalides (1982) and Burghuber et al. (1986). These studies, described in Cal/EPA (1997), document a significant decrease in platelet sensitivity to the anti-aggregatory effects of PGI2 among nonsmokers but not active smokers following acute smoke exposure. Since this volume is meant as a supplement and update to the 1997 document, we have not reviewed material previous examined other than where it was felt essential for the readers understanding.

Comment 35

All in all it is a very good report.

Response:

Thank you for your comments.

Comments of Katharine Young

Comment 1:

There have been a number of recent reviews of the association between SIDS and parental smoking[1,8,20,28]. When attempting to interpret the results relating to ETS exposure it is important to bear in mind the following points:

Some of the studies[10,11,13,25] reporting an association between SIDS and ETS exposure have not adjusted for any other risk factors, while many others[9,12,14,16,17,21,23,26,27] have only taken a few of them into account.

Response:

Consideration of other risk factors is a critical concern, especially in many of the older studies mentioned above. In general, the more recent studies included in this update had better control for confounding and continued to support a causal association.

Comment 2:

Four studies[15,18-20] have taken into account quite an extensive list of potential confounding variables in at least some of their analyses. In two studies[15,20], such adjustment explained about 80% of the increased risk of SIDS associated with maternal smoking after pregnancy, and in a third study[19] it explained about 50%. In the fourth study[18], adjusted results were not reported for maternal smoking after pregnancy, but adjustment markedly reduced the relative risk associated with maternal smoking in pregnancy, from 4.84 to 1.78. Since such adjustments will inevitably be incomplete - partly because not all such factors will have been considered, and partly because data errors or use of surrogate variables limit the ability to control for confounding - it is not implausible that all of the claimed SIDS/ETS association could in fact be explained by confounding.

Response:

Newborns are indeed vulnerable to a variety of environmental conditions that may contribute to SIDS, adjustment for which reduces the apparent risks associated with ETS. However the consistency of the association of SIDS with ETS exposure in a variety of studies after adjustment for multiple confounders reduces the plausibility that the SIDS/ETS association is wholly explainable by confounding. Furthermore, adjustment for all confounders is nearly impossible, and may actually result in over-controlling for confounders masking the ETS effect.

Comment 3:

In a recent study[29], infants with prolongation of the QT interval, as measured by electrocardiograph shortly after birth, had a more than 40-fold increased risk of SIDS. This abnormality, seen in 50% of the infants dying of SIDS, is a major risk factor that could not have

been caused by postnatal ETS exposure and which has not been taken account of in any of the epidemiological studies of ETS and SIDS.

Response:

Recent experiments in rats may provide a link between an infant's smoke exposure in utero and prolonged QT interval. Alterations in cardiovascular responsiveness to neurotransmitters were seen in rats after prenatal exposure to nicotine at levels consistent with maternal smoking (Slotkin et al., 1999). This exposure was associated with an increase in cardiac muscarinic type 2 receptors (M2) on which acetylcholine acts to decrease contraction rate. Nicotine exposure has been shown previously to cause a decrease in ß-adrenergic receptors (Navarro et al., 1990) through which heart rate is stimulated. The combination of an increase in inhibitory receptors and a decrease in excitatory receptors would be expected to lead to dis-regulation of heart function, possibly manifesting as an increased QT interval. This study also reported a nicotine-induced reduction in brainstem muscarinic receptors paralleling that seen in infants who have died from SIDS. In these infants there was decreased binding in brainstem areas associated with cardiorespiratory functions (Kinney et al., 1995). Thus ETS exposure may contribute to the risk of SIDS by impairing the ability of the brain and heart to respond appropriately to periods of hypoxia especially in infants exposed to smoke components in utero.

Comment 4:

Even if the association between parental smoking and SIDS cannot fully be explained by uncontrolled confounding by other risk factors, it may result, not from ETS exposure but from an effect of maternal smoking in pregnancy. Some studies have found that the association of SIDS with postnatal maternal smoking or paternal smoking has been reduced[15,16,20] or even eliminated[21] if adjustment is made for maternal smoking in pregnancy or if attention is restricted to nonsmoking mothers, though others have not[14,19].

Response:

Infants whose mothers smoked during pregnancy are indeed at greater risk of dying from SIDS; however, postnatal ETS exposure is an independent risk factor that can exacerbate this effect. Thus a reduction in the apparent SIDS risk after adjustment for maternal prenatal smoking would be expected. Our estimate of SIDS risk for maternal postnatal smoking is from a meta-analysis of studies that controlled for maternal prenatal smoke exposure (Anderson and Cook, 1997). Yet higher risks (OR 3.50) and a dose response were found by Klonoff-Cohen et al (1995) for postnatal ETS from all sources after adjusting for maternal prenatal smoking and other risk factors.

References used in responses:

Anderson HR, Cook DG (1997). Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. Thorax 52(11):1003-9.Lee reviewed 956.

Kinney HC, Filiano JJ, Sleeper LA, Mandell F, Valdes-Dapena M, White WF (1995). Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. Science 269(5229):1446-50.

Klonoff-Cohen HS, Edelstein SL, Lefkowitz ES, Srinivasan IP, Kaegi D, Chang JC, et al. (1995). The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. JAMA 273(10):795-8.

Navarro HA, Mills E, Seidler FJ, Baker FE, Lappi SE, Tayyeb MI, et al. (1990). Prenatal nicotine exposure impairs beta-adrenergic function: persistent chronotropic subsensitivity despite recovery from deficits in receptor binding. Brain Res Bull 25(2):233-7.

Slotkin TA, Epps TA, Stenger ML, Sawyer KJ, Seidler FJ (1999). Cholinergic receptors in heart and brainstem of rats exposed to nicotine during development: implications for hypoxia tolerance and perinatal mortality. Brain Res Dev Brain Res 113(1-2):1-12.

Comments received after the SRP meeting on Tuesday, November 30, 2004, with responses presented to the SRP at subsequent meetings

Comments of Robert T. Croyle, Ph.D. (Director, Division of Cancer Control and Population Sciences, National Cancer Institute)

Comment 1:

The California EPA's report on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant provides an excellent discussion of findings on the health effects of ETS. The Division of Cancer Control and Population Sciences of the National Cancer Institute appreciates the opportunity to review and comment on this report. The authors of the report should be congratulated on this achievement. The California EPA's previous report has served as an authoritative reference document on ETS and health effect, and this new report is likely to become widely read and cited. Two important changes in the new report are the designation of ETS as causes of nasal and breast cancers. This is in contrast to the findings of the International Agency for Research (IARC) in 2002. Although the IARC report in the monograph series Evaluation of the Carcinogenic Risks to Humans, Tobacco Smoke and Involuntary Smoking, Volume 83 is not yet published in book form, the summary conclusions are available at the agency's website: http://monographs.iarc.fr/htdocs/indexes/vol83index.html. In view of the differences between the conclusions of two reports and the public health implications of the new designations by the California EPA of ETS as causal factors in the etiology of particular cancers, the National Cancer Institute, part of the National Institutes of Health, strongly recommends the appointment by the California EPA of an expert panel representing the appropriate disciplines to review and to come to a consensus on the evidence on ETS and cancer.

Response:

Thank you for your comments. Our document is peer reviewed by the State's Scientific Review Panel on Toxic Air Contaminants, a body created under state law to provide independent scientific review of documents produced by CalEPA. It is composed of 9 independent scientists nominated by the President of the University of California from the disciplines of pathology, oncology, epidemiology, biostatistics, toxicology, occupational medicine, atmospheric chemistry, biochemistry and molecular biology, and other relevant disciplines. They consider both the document prepared by ARB and OEHHA as well as all the public comments and responses to those comments as part of the peer review process. If the Panel wishes they may consult additional experts during their review process.

There are a 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 that were unavailable to IARC at the time of their review. OEHHA staff and consultants also undertook different (and more extensive) analyses of data than those used by IARC

The designation as a causal factor for nasal sinus cancer is not a new finding and was found originally in the 1997 document (CA EPA, 1997). As noted below in the response to comment

two, we have now separated nasopharyngeal cancer into a separate section with findings distinct from those of nasal sinus cancer.

Some specific comments on Chapter 7 Carcinogenic Effects:

Section 7.3.1 Nasal sinus cancer

Comment 2:

The studies listed under nasal sinus cancer appear to be for nasopharyngeal cancer, a different anatomic site than nasal cancer, a term that typically refers to cancers of the nose and paranasal sinuses.

Response:

The comment is correct and the text has been changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. Nasopharyngeal is now listed as a separate category with the finding of evidence suggestive of a possible association.

It is of interest to note that in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002) report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS also would have similar effects in both sites.

As mentioned in our response to comments by M. LeVois, 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 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, but 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 suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Section 7.4.1 Breast Cancer

Comment 3:

More weight should be given to the recent published findings from cohort studies in view of their large size and ability to clearly establish exposure as occurring before recognition of the cancers.

Response:

The recent cohort study by Reynolds et al. (2004) has been added to the review. Although cohort studies in general have the potential to be preferable for examination of risk, all of these studies

suffer from seriously incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Rothman and Greenland (Modern Epidemiology, 2nd edition). A fundamental requirement for study validity is a level of accurancy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all of the sources of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontham et al (1994), which is a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements for exposure assessment. While it is true that in the prospective studies exposure is ascertained prior to disease onset and that this is a desirable feature, exposure during the critical period of adolescence and young adulthood is obtained by retrospective history, since enrollment is typically well beyond that time in life. So, exposures that may be occurring during critical windows (e.g., peripubertal, prior to first pregnancy) for breast cancer are obtained retrospectively in both case-control and cohort studies, and the benefits of a prospective cohort study are thereby lessened. As well, typically the cohort studies identify exposure at a single timepoint at the onset of the cohort study which has been shown to have significantly reduced predictive value in a study of ETS and cardiovascular risk (Whincup et al., 2004). The problem of reporting bias related to retrospective studies is mitigated as the potential link of smoking or ETS to breast cancer has not been well accepted in the scientific literature and is not commonly known to the public.

Comment 4:

The meta-analysis from the Collaborative Group Study of Breast Cancer, Alcohol, and Smoking used a simplistic characterization of active smoking in their analysis - ever/never and current/ex-smoker - however, it is not clear why this variable would be considered by the California EPA authors as "poor quality".

Response:

Comparing ever to never smokers (whether current or former) is a very crude estimate of exposure. There is no attempt to quantify the degree of exposure in this analysis. One of the paper's main limitations is the inability to consider in its analysis exposure to environmental tobacco smoke. The above mentioned pooled analysis makes no claims of considering passive smoke exposure in any way. Under the methods section they state; "no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure". If, as we believe to be true, the data support a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason), and if most non-smokers have had significant ETS exposure, which is certainly the case particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk.

Additionally, several recent papers suggest positive associations emerging after 30- 40 years smoking duration (Terry and Rohan 2002, Johnson et al., 2003, Reynolds et al. 2004); association with years of smoking prior to first pregnancy (Band et al. 2002, Terry and Rohan 2002, Eagan et al. 2002, Johnson et al. 2003, Reynolds et al. 2004) or onset smoking at earlier age (Eagan et al. 2002, Calle et al. 1994, Reynolds et al. 2004). The analysis by the

collaborative group is unable to account for these time-dependent associations noted in various studies.

Passive smoking has been shown to be associated with alcohol consumption (Reynolds et al. 2004, J Women's Health). In our analysis of passive smoking there is an associated risk that exceeds that identified with alcohol. Since the pooled analysis did not include information about passive smoking, it is unable to untangle the degree to which the reported association with alcohol may in fact be due to its correlation with passive smoke exposure. Johnson (2000), Kropp and Chang-Claude (2002), Marcus (2000) and Morabia (1996) are examples of studies that found little or no modification of risk when adjusting for alcohol consumption.

Section 7.4.1.3 Active smoking and breast cancer.

Comment 5:

The first paragraph that precedes the discussion of individual studies appears to be a partial summary, but it does not synthesize the information and may be misleading. For example, it appears that positive findings that appear only in a subgroup are not labeled as such. The Egan study is said to show an association in either active or former smokers. However, that study showed no overall association of smoking and breast cancer among current smokers (RR=1.04) or ex-smokers (1.09) and so the authors probably were referring to active and former smokers among a subset of the women.

Response:

This sentence will be altered to read, "These studies indicated an increased risk, either overall or in some subgroupings…".

Comment 6:

This section needs a synthesis that assesses the body of epidemiological evidence. Since the findings for the active smoking section presumably are included to provide evidence about the plausibility of the findings for passive smoking and to set the stage for discussions about consistency with ETS findings, there probably should be a synthesis section for each active smoking section with updated information/studies. The synthesis should clearly distinguish overall findings for smoking and breast cancer from findings in specific subgroups.

Response:

Additional discussion and summary have been included under section 7.4.2.5.1, Relative Potency of Active and Passive Smoking. The tables included in the active smoking section do present overall findings as well as those for various subgroupings. As you note, the main purpose of including the active smoking studies was to inform the discussion of passive smoking in light of the widely held belief that the accumulating data associated with passive smoking was inconsistent with active smoking data. The addition of Reynolds et al. (2004), a U.S. based cohort study, has further strengthened the evidence that active smoking is in fact associated with

increased risk as well as passive smoking. Since the discussion was included as supportive evidence, a less complete discussion of active smoking has been presented in the document.

Section 7.4.1.4. ETS and breast cancer.
Section 7.4.1.5.

Comment 7:

A new study that could be included here is: Gammon MD et al., Environmental tobacco smoke and breast cancer incidence. To be published in Environmental Research in 2004, but available now through Science Direct.

Response:

Thank you. This new study has been added.

Comment 8:

The citation to Terry et al., 2002 on page 7-122 is incorrect. This study does not address passive smoking and breast cancer, only active smoking.

Response:

Thank you. This has been corrected and moved to the appropriate section on active smoking.

Comment 9:

There is a reference to a paper by Zhao in 1999 in Table 7.4F. However, this study is not described in text and the reference does not appear in the list of references.

Response:

Thank you. A description of the study has been added.

Section 7.4.1.6.

Comment 10:

This section is labeled as a summary of the evidence regarding ETS, but it focuses only on the possible explanations of findings reported in the previous CalEPA report and does not address findings since then. Have the limitations to the interpretation of the findings in the previous CalEPA report been fully addressed in the more recent studies?

Response:

This section (as well as several subsections under it) has been expanded and relabeled to more accurately identify topics discussed. "Limitations of the studies" has an expanded discussion. It

is our premise that many of the limitations of the previous studies reviewed in the 1997 document have been well addressed in the studies subsequently and particularly in those categorized by us as "unlikely to have missed important measures of ETS exposure" in Table 7.4.1R of the current version.

Comment 11:

Overall risks associated with passive smoking and dose response relationships should be summarized, then focus on subsets (e.g., pre- and post-menopausal), providing risks for the subset and, where available, dose-response relationships for that subset.

Response:

We have done this in the report, primarily by summarizing the data in tables and noting in the text when there was evidence of effect in specific subsets and evidence of dose-response.

Section 7.4.1.7: Consistency. (Starting on page 7-136)

Comment 12:

This section addresses the qualities of the most recent studies, not the consistency among them. To address consistency this section should include an evaluation of agreement among the studies of ETS, including across subgroups defined by biological characteristics (e.g., menopausal status) as well as the consistency with findings for active smoking as well as the consistency of findings within studies that examined both active and ETS.

Response:

Consistency refers to repeated observation of an association in different populations under different circumstances (Rothman and Greenland 1998, pp 24-28). We are aware that total consistency of findings across studies is both difficult to evaluate (due to differing methodologies as well as random errors) and difficult to present since metrics evaluating exposure and risk vary from study to study. As the causal mechanism is not fully elucidated, studies have investigated various hypotheses. According to Rothman and Greenland (1998), "Consistency is apparent only after all the relevant details of a causal mechanism are understood, which is to say very seldom."

Despite these difficulties, this section summarizes some of the ways in which repeated associations between environmental tobacco smoke exposure and development of breast cancer have been demonstrated over time and across studies in different countries. We have attempted to further demonstrate the increased consistency of findings when studies have done a better job of measuring lifetime ETS exposure (presented in figure 7.4.2).

Overall, in our analysis, the studies of breast cancer are a heterogeneous group. When we restrict the studies to those with better exposure measurements (including childhood, adult residential and workplace exposures), the test for homogeneity is consistent with a homogeneous grouping and the risk estimates are higher.

Section 7.4.1.7: Strength and specificity.

Comment 13:

Recommend addressing overall risks associated with passive smoking and the dose-response relationships curve overall, then focus on subsets of women (e.g. pre and post menopausal) providing the risks for the subset and the dose response for that subgroup, if available. This is an important distinction because a finding that is homogenous across subgroups and shows a dose response relationship must have a different biological mechanism than one that is confined to women with particular biological characteristics (e.g., particular types of tumors, women with particular biological characteristics such as menopausal status).

Response:

We have done this in the report, primarily by summarizing the data in tables and noting in the text when there was evidence of effect in specific subsets and evidence of dose-response.

We do not agree with the premise in the last sentence. The response of breast cancer risk to ETS exposure appears both in the overall data and in the various subgroups. The degree of response may vary between subgroups, so that it is more likely that a statistically significant effect will be observed in the more sensitive subgroups. However, we do not see any indication of absolute non-responsiveness in certain subgroups, and have therefore not emphasized this type of analysis.

Table 7.4.G.

Comment 14:

Add a table on post-menopausal findings. This would be useful for assessing consistency of findings.

Response:

A table will be added to the final report and provided to the Scientific Review Panel.

References:

Rothman KJ, Greenland S. (1998) Modern Epidemiology, second edition. Pp 24-28. Lippincott-Raven Publishers, Philadelphia.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ. Jul 24;329(7459):200-5.

These and other references noted are cited in the document.

Response to Further Comments on California EPA draft Health Effects Assessment for ETS submitted by Michael J. Thun, M.D. (May 2, 2005) American Cancer Society, Atlanta, GA.

OEHHA May 26, 2005

Comment 1:

I have reviewed the March, 2005 draft of the California Environmental Protection Agency (Cal/EPA) evaluation of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (*1*). The Agency is to be commended for revising the draft extensively in response to public comments. At this point I still consider the evidence that tobacco smoke increases breast cancer risk to be limited rather than sufficient, according to the IARC criteria. This is not the same as rejecting the possibility that ETS and/or active smoking may affect breast cancer risk. It means only that the currently available evidence for this is limited.

I am concerned that, despite the revisions, this draft of the report still describes the evidence concerning breast cancer in a manner that overstates its strengths and minimizes its limitations. This weakens rather than strengthens the effectiveness of the report in my view. At present, the conventional wisdom among breast cancer researchers is that tobacco smoke (either as active smoking or as ETS exposure) has not been shown to affect breast cancer risk. If OEHHA wishes to change this, it must discuss the available evidence accurately and objectively, acknowledging both its strengths and limitations. The report must seriously consider alternative hypotheses that might explain the association observed in case-control studies, and demonstrate that these cannot account for the findings. The present draft does not do this.

Response:

We do not believe we are overstating the strengths of the evidence on the association between ETS exposure and breast cancer risk. In the latest draft, which addresses many of the concerns Dr. Thun has raised, we have provided more discussion of the strengths and weaknesses of the overall data and the data specifically on breast cancer in younger primarily premenopausal women, and have elaborated more on our conclusions. We do not think all breast cancer researchers disagree with our conclusions. In addition, many have not closely examined the literature upon which our findings are based. We feel that the latest (May, 2005) revised version of the document does a better job of describing our considerations of alternative hypotheses that might explain the association observed and demonstrating why they are unlikely to account for the findings.

Comment 2:

A broader issue, beyond the strengths and limitations of the studies on ETS and breast cancer, concerns how CalEPA addresses the issue of uncertainty. Irrespective of whether or not tobacco smoke causes breast cancer, the available data leave much room for uncertainty. Proponents of the concept that ETS exposure causes breast cancer argue that undue delay is more harmful to progress in tobacco control than is the opposite – concluding that ETS causes breast cancer when it is does not. I strongly disagree. I believe that a major policy reversal with respect to ETS and breast cancer would be far more damaging to the scientific credibility of tobacco control efforts – especially those based on other harmful effects of ETS - than a deliberative approach that acknowledges the limitations of the evidence currently available. Furthermore, as discussed below, I see no reason why CalEPA cannot draw attention to the potential link between ETS and breast cancer without concluding that the current evidence is sufficient.

Response:

OEHHA is responsible for conducting risk assessments of a broad number of environmental contaminants, and takes a health-protective approach in assessing risks and potential public health impacts. In every health effects assessment there is at least some uncertainty, the degree of which varies widely. Many times, we have only animal data and not human epidemiological, clinical or experimental data. In the case of ETS, we are basing conclusions on epidemiological data for each health outcome with support from existing toxicological data, standard risk assessment practice. We recognize that there is uncertainty in the evidence pertaining to the association between ETS exposure and breast cancer risk. However, there is in our view, sufficient evidence from a number of studies evaluating humans experiencing real-world exposures indicating an association between ETS exposure and breast cancer risk, particularly when diagnosed in younger primarily premenopausal women.

We have looked at uncertainty in several ways in our analysis, both qualitatively and quantitatively. First, where there are inconsistencies in study results, we evaluated possible reasons for the inconsistencies. Second, we focused on study quality and find that exposure assessment is critical, and that the difficulties with ascertaining exposure to ETS over all sources and over the lifetime is not trivial and impacts study results. Some studies have done a better job than others in this regard. Those studies that attempted to ascertain exposure over a lifetime from multiple studies are given more emphasis in our analysis. Third, we considered the reported risk estimates and their 95% CI for each study. We conducted meta-analyses of the epidemiological studies that met minimum criteria both for overall (all age women), and for younger primarily premenopausal women. In both cases, we obtained pooled risk estimates above 1 that were statistically significant. The risks for younger primarily premenopausal women were higher and in the studies that did the best lifetime exposure assessment, the risks are above 2. Thus, we also quantitatively considered uncertainty in the evidence.

Comment 3:

The discussion of the overall evidence on page 7-132, pp 1, lines 1-4 begins with the statement "..recent, primary, population-based case control studies (as well as three cohort studies) … have consistently identified elevated breast cancer risks for residential and occupational exposure overall, or in individual strata." This is misleading, in that it implies rapid accumulation of evidence supporting the hypothesis. In reality, Figure 7.4.4 indicates that eight of the ten studies published from 2000 to 2005 report relative risk estimates for overall breast cancer in ETS exposed women near or below the null. The qualifier "or in individual strata" may be accurate, but subgroup findings do not constitute "consistent" support for the main hypothesis. As seen in Figure 7.4.4, nine studies published from 1984 to 1999 reported RR estimates of 1.3 or greater for breast cancer in ETS exposed women. These studies drew attention to the possibility that ETS exposure might increase breast cancer risk. However, most studies conducted since the year 2000 have largely been unable to replicate the main finding. This temporal pattern should not be interpreted as rapidly accumulating support for the hypothesis. Rather, it is a reason to reexamine all of the data critically to identify possible sources of inconsistency.

Response:

The comment refers to an introductory paragraph summarizing the evidence of an association between ETS exposure and breast cancer risk overall. The term "recent" was used in the sentence originally because we meant to distinguish between the 4 studies reviewed in our earlier 1997 report and the additional 22 studies reviewed in this update. This has resulted in much confusion to Dr. Thun and others when examining the results for "overall" (all women, nonstratified), since several post-2000 studies do not find an overall association. However, many of these studies examining risk in younger (primarily premenopausal) women did find elevated breast cancer risk for this stratum. We have removed the term "recent" to avoid this confusion.

In the sentence in question, "individual strata" includes the results from studies reporting on risk to younger, primarily premenopausal women. In the previous version on which Dr. Thun is commenting we had tried to make clear that the conclusions were "primarily based on the strength of evidence in younger women (<50 years) diagnosed prior to menopause". Since some confusion has remained, the emphasis and conclusions of the document have been further clarified to state that the evidence from the reviewed studies support a conclusive finding for ETS and breast cancer in younger (primarily premenopausal) women but not for postmenopausal women. In Comment 10, Dr. Thun concedes that "the subgroup of studies on premenopausal breast cancer deserves to be singled out". Since the main hypothesis has now been clarified as the association between ETS exposure and development of breast cancer in younger primarily premenopausal women, this subgroup analysis (which finds relatively strong associations which are consistent across study design and region) can be said to provide consistent support for the main hypothesis.

We have reworded the introductory paragraph that Dr. Thun is commenting on to read as follows:

> *"Many population-based case-control studies (as well as three cohort studies), controlling for several important reproductive, dietary and other potential confounding factors, have identified elevated breast cancer risks for residential and occupational exposure overall or in individual strata. Higher risks were noted in several studies for breast cancer diagnosed in women under age fifty (primarily premenopausal), or with long duration or high intensity exposure. The toxicological data on carcinogenicity of tobacco smoke constituents (see Table 7.4.1E) strongly support that the risk associated with ETS exposure is highly plausible."*

As noted in the above response, OEHHA has clarified the basis of the causal conclusions in the latest draft to indicate that it applies to younger primarily premenopausal women. Looking at figure 7.4.5 which illustrates the reported risk estimates for ETS and premenopausal breast cancer, only one study of 14 illustrated (including 7 studies from 2000 on) does not report an estimate greater than one (Reynolds et al., 2004). It should be noted (as we did in the response to Dr. Thun's original comments) that Reynolds examined only household exposure to ETS, and that she notes that from the early 1980s on, sources of ETS exposure for U.S. women have been documented to have come primarily from outside the home (i.e., at work). In addition, the designation of menopausal status in Reynolds results is determined by history as pre or peri-menopausal at enrollment not at diagnosis. Certainly many of those who were peri-menopausal at enrollment turned postmenopausal during the four years of followup. Assuming that our interpretation of the data is correct (that risk estimates are increased by examining all sources of exposure, and are highest in younger primarily premenopausal women), Reynolds study is subject to two forms of misclassification (exposure and age at diagnosis) that would each bias towards the null.

Of the 14 studies reporting risk estimates for breast cancer in younger/premenopausal women in figure 7.4.5, seven report statistically significant associations.

Comment 4:

1) OEHHA attributes the negative findings of recent studies to misclassification of ETS exposure, and inclusion of ETS exposed women in the referent group. However, at least two of the negative studies during the latter interval (Reynolds et al 2004 and Gammon et al 2004) excluded from the control group persons who reported ever living with a smoker. If there is in fact a dose-response increase in breast cancer risk with increasing duration of ETS exposure (as discussed below), the exclusion of women with any household exposure should allow higher breast cancer risk to be evident in women with long-term household exposure to ETS. However, in the Reynolds study, only active smoking is associated with breast cancer risk, and this association is unaffected by inclusion or exclusion of women with household ETS exposure from the referent group.

Response

As discussed in the document, and noted in our previous response to Dr. Thun's original set of comments, OEHHA believes (and demonstrates) that it is important to include all sources of exposure to ETS to determine the association between ETS exposure and breast cancer. Reynolds examines only residential (lifetime) and Gammon only adult residential ETS exposure. It would be important to consider the relative contribution from various sources of exposure (adult, child, residential, occupational, and other) to overall lifetime exposure in order to estimate the likelihood that examining only residential exposure would show a response. Within the California Teacher's Cohort (Reynolds et al., 2004) from the early 1980s on, sources of ETS exposure have been documented to have come primarily from outside the home. In addition, Friedman et al. (1983) found that using spousal smoking to classify persons as ETS-exposed resulted in considerable misclassification in both directions. Forty to fifty percent of persons with non-smoking spouses reported passive smoke exposure and as many as thirty five percent of those married to smokers reported no exposure. If the primary source of the exposure of interest is found equally in the cases and controls (a result of misclassifying those exposed to ETS at work or outside the home as unexposed), it would be understandable that a study might fail to identify an effect.

Comment 5:

If the absence of data on "important ETS exposures" accounts for the null findings of most of the studies published since the year 2000, it is not clear why all of the studies published before 2000 found a relatively strong association between ETS and breast cancer, even though six of these were also missing data on "important ETS exposures" (Table 7.4.1.B). The OEHHA report attributes the heterogeneity of the published studies to variations in the accuracy with which ETS exposure is measured. The report fails to consider inconsistencies in this hypothesis, and does not devote serious consideration to the possibility that the heterogeneous results may result from other unmeasured factors that are correlated with but separate from ETS exposure.

Response

Of eight studies examining breast cancer risk in younger primarily premenopausal women from 2000 onward, seven have elevated point estimates and four are statistically significant. There are myriad reasons that one might postulate regarding why some studies found positive results and others not, and we think that exposure misclassification is one of them. We do not imply that this is the only reason. If, as we believe, the risks are more evident in premenopausal or younger women, the relative age distribution in a study population would be a key factor in the ability to demonstrate an association. Many studies do not report that information. Further, in studies that did the best job of ascertaining lifetime exposures to ETS from all sources (residential, occupational, other), and that had, as a result cleaner referent groups, risk estimates were highest and statistically significant for younger women. It is difficult to ascribe these higher estimates to unknown or uncontrolled-for confounding, particularly since these studies generally attempted to account for major known risk factors. All of the six studies

considered by OEHHA as most informative considered, and adjusted in the final model when appropriate, measures of reproductive factors (parity, age at first childbirth, age at menarche, etc.), alcohol consumption, and oral contraceptive use. Four or five of six studies also controlled for BMI, SES (or surrogates), breastfeeding, and family history.

Comment 6:

2) A central tenet of the OEHHA report is that a small amount of tobacco smoke (at levels consistent with ETS exposure) increases breast cancer risk, but that greater exposures, or at least those incurred from active smoking, do not further increase risk. The magnitude of the effect of passive smoking is said to be similar to that of active smoking. While this hypothesis may be biologically possible, it is not typical for a dose-response relationship, and requires further supporting evidence to convince skeptics. It may be that "OEHHA prefers to characterize non-linearity of the dose-response for breast cancer to tobacco smoke as an observation, not a theory" (response to my 6th comment on the previous draft). However, unless there is good evidence to account for this observation, breast cancer researchers will continue to see the unusual dose-response relationship as an important limitation in the evidence.

Response:

There are actually two main issues that need to be pointed out (and have been in the document). The first is that it is more important to look at dose-response evidence within passive and active smoking studies than between them. ETS and mainstream smoke are not identical, and the exposures of passive smokers and active smokers to specific toxicological substances found in tobacco smoke are different.

Secondly, if one compares risk of breast cancer from passive smoking and active smoking, then the risks appear to be about the same. This is an observation, not a theory. The observation of the non-linear dose response to tobacco smoke (between active and passive smoking) for breast cancer is based on evidence from those studies which characterize ETS exposure fully. Non-linear dose response relationships are not remarkable or unusual, and are routinely seen in toxicological studies. Epidemiological analyses are frequently confined to the assumption of a linear dose-response, but this is often due to the insufficient power of the study to determine a more complex relationship from the data, rather than actually providing evidence of linearity. Some non-linear epidemiological dose-response relationships have been demonstrated however. Indeed, the relationship between active smoking and lung cancer is an example where although at low to moderate dose levels the response is generally concluded to be linear with smoking duration and intensity, a flattening of the response curve is seen at the highest dose levels (Ruano-Ravina et al., 2003).

The similarity of risks between active and passive smoking in breast cancer mirrors the findings with cardiovascular disease. For some cardiovascular health outcomes, the risk from ETS exposure is more pronounced than would be anticipated from studies of active smokers. These effects include both death from CHD, which involves both chronic and short-term exposures, and measurable vascular changes from short-term smoke

exposure. Many of the same arguments proposed as explanations for the similarity of active and passive smoking risks in cardiovascular disease, examined in an excellent paper by Drs. Howard and Thun (1999), hold true for breast cancer as well. These include the much higher levels of many constituents of smoke in ETS than in mainstream smoke. In addition in the case of breast cancer, the anti-estrogenic action of active smoking may play a confounding role by partly mitigating breast cancer risk. In at least two of the ETS/breast cancer studies we examined (Egan et al., 2002, Gammon et al., 2004,), as well as in previous literature (Baron et al., 1990), women entered menopause up to 2 years earlier if they were active smokers partially mitigating breast cancer risk. The Surgeon General's report (2004) on active smoking notes the potential competing effects of anti-estrogenicity and carcinogenicity on breast tissue in active smokers. As Howard and Thun (1999) conclude: "Because ETS affects multiple physiologic pathways, it is entirely plausible that the dose-response relationship is not linear over the entire range of exposure".

Comment 7:

a. The OEHHA report seems internally inconsistent with respect to the presence or absence of a dose-response relationship. Page 7-132, paragraph 2 argues that there is "a positive dose-response relationship [between breast cancer risk and] passive smoking". Table 7.4.1J presents data from seven studies supporting this view. Nevertheless, the null results of cohort studies published by Reynolds et al.(2004), Egan et al. (2000), and Wartenberg et al. (2000) are dismissed as invalid because they only measured ETS exposure in adulthood, not in childhood. If it is true that the duration of ETS exposure is important, then studies that assess the duration of exposure in adulthood should be able to detect increased risk associated with long term exposure.

Response:

We do not believe the report is internally inconsistent with respect to evidence for a dose-response. Obviously, not all studies found evidence of a dose-response, but several studies report a dose-response gradient, based on overall dose as a function of both duration and intensity (consistent with findings at other sites, e.g. lung, by IARC [2004]) (Section 7.4.1.4.2). We do not dismiss the cited cohort studies because they only measured ETS exposure in adulthood and not childhood. Rather, we considered the exposure ascertainment incomplete in several studies including these. Limited exposure ascertainment, a problem with ETS in particular and environmental epidemiology studies in general, clearly diminishes the ability to detect an effect and to find a dose-response gradient. The importance of exposure during childhood relates to the timing (windows of susceptibility), not only the duration, of the exposure. It should also be noted that Reynolds, Egan, and Wartenberg were weighted in the lower tier of studies as a result of more than just the failure to account for childhood exposure (Reynolds in fact does and Egan does but does not present a combined analysis of risks from both childhood and adult exposures). None of these three studies utilizes methodology that allows for lifetime exposure from all sources.

In particular, regarding limitations of these studies in determining premenopausal risk: 1.) Reynolds is discussed above; 2.) Egan does not provide data on menopausal status or risk; 3.) Wartenberg, which evaluated death rather than diagnosis as the endpoint, provides data for women under age 50 from which we calculated our "premenopausal" estimate. The age 50, however, is at baseline not at diagnosis. The paper does state that 75% of women in this study were between 45 years and 70 years at enrollment and that the median age was 56 years at enrollment. The cohort was followed for 12 years likely allowing a substantial portion of the women that we included as premenopausal (under age 50 based on information at baseline) to have actually been postmenopausal at death. Reynolds suffers from a similar problem in the analysis as is discussed above.

Not all cohort studies have failed to find an association between ETS and breast cancer. Three Asian cohorts have reported elevated risks (Hirayama 1984, Jee et al. 1999, and Hanaoka et al. 2005). OEHHA argues that limited exposure assessment may be part of the reason for the inconsistencies seen among the cohort studies (Hanaoka et al., 2005 had the best exposure assessment of all the cohorts and found elevated statistically significant breast cancer risk in premenopausal women) and case-control studies. The null result in, for instance, the study by Wartenberg et al. is exactly what would be expected for a relatively small magnitude association such as between ETS and breast cancer, given the limited exposure assessment and the likely exposure misclassification in the referent population.

Finally, we did not "dismiss" any of the cohort studies, but rather evaluated reasons for inconsistencies including the overall quality of exposure assessment, which is found to be problematic for most of the cohort studies. The three studies mentioned in the comment, Reynolds et al. (2004), Egan et al., (2002), and Wartenberg et al. (2000), were included in the meta-analysis of overall breast cancer risk (which obtained a pooled estimate of 1.25 (1.08-1.44)), and both the Reynolds and Wartenberg papers were included in the analysis of pre-menopausal risk, as we were able to pull out data for younger/premenopausal (at baseline) women from these studies. In those meta-analyses, these studies were heavily weighted because of their large sample size. The meta-analysis for younger primariy premenopausal women had a pooled estimate of 1.68 (1.31-2.15) including those studies which had limited exposure assessment. Excluding studies with relatively poor exposure assessment resulted in elevated risk estimates for breast cancer in younger primarily premenopausal women, as one would expect.

Comment 8:

b. The potential for recall bias and uncontrolled confounding is particularly great in case control studies in which the referent group is restricted to women who report no active smoking and no ETS exposure in either childhood or adulthood. These women generally constitute between 10% and 25% of potential controls and may or may not differ from other women on factors related to breast cancer risk (published data only provide information on all cases and all controls, not on this relevant subgroup). Although studies vary in the extent to which they control for covariates, none of the studies control for mammography (which the affects the age at which breast cancer is diagnosed as well as overall incidence); only the

cohort studies control for post-menopausal hormone use. Some studies control for alcohol consumption only as "ever – never" and for reproductive factors only in broad categories. Women who report no ETS exposure may be more likely to work at home, to be relatively isolated, and/or to belong to special religious groups. All of these attributes may influence other factors related to breast cancer. However, none of the published studies provide information on the demographic and other characteristics of this subgroup that is reputed to be the only appropriate referent group.

Response:

As we noted in the response to Dr. Thun's original comments women who report no active smoking and no ETS exposure in child or adulthood represent more significant proportions of potential controls in many studies than he indicates above. The table below is excerpted from that previous response.

Study	Cases not exposed to ETS	Controls not exposed to ETS
Hirayama	20%	24%
Sandler	41%	57%
Smith	5%	13%
Morabia	22%	39%
Milikan	36%	35%
Lash 1999	34%	33%
Delfino	52% (low risk pool)	73% (low risk)
Zhao	35%	56%
Jee	No data available (NDA)	NDA
Johnson	11%	17%
Nishino	70%	58%
Kropp	22%	32%
Lash 2002	26%	21%
Egan	9.8% (low risk)	NDA

We agree with Dr. Thun that an analysis of the demographics of never smokers that have not been exposed to ETS (or been minimally exposed as in the stabilized Johnson analysis) would be valuable and to date has not been provided. However, since the studies noted have been conducted in various countries throughout the world, it seems unlikely that the demographics of women with minimal exposure to ETS (constituting between 13% and 56% of non-smoking women controls in studies with lifetime unexposed referents) can be explained by social or religious factors. The association noted for younger primarily premenopausal women is found in nearly all of the studies that examined this strata, regardless of whether they utilized a definition of unexposed that included only those who had no reported lifetime exposure or not. It is preferable to utilize an analysis that excludes as much as possible those with known exposure to the substance of concern from the control group, rather than knowingly include ETS exposed

individuals in the control group because of a hypothetical concern about potential confounding.

Of the 5 better case-control studies that used better exposure assessment (as defined in section 7.4.1.3 OEHHA Summary Risk Estimates), 2 suggested dose-response relationships and 3 had overall ORs over 2.3. The 3 Asian cohort studies suggested positive dose-response relationships and the two recent large American case-control studies (Shrubsole and Gammon) each suggested increased risk in the highest ETS exposure category. We would suggest that putting a larger percentage of women in the referent group (for example, adding those with a history of limited exposure to ETS) would be likely to simply dilute overall risks, reduce the risk in the highest exposure category, or reduce the steepness of the dose-response gradient. However, adding those mildly exposed to the unexposed in order to have a larger percentage of women in the referent group would be unlikely to change the overall dose response pattern noted of increased risk with higher or longer duration exposure.

Comment 9:

3) The current draft still overstates the significance of currently available data on subgroup analyses, particularly with respect to genetic polymorphisms and gene-environment interactions. For example, page 7-145, lines 7-5 from bottom states that such analyses provide evidence for "..highly significant increased breast cancer risk associated with active smoking ". This overstates the importance of the data from Crouch et al. 2001. There is actually widespread skepticism about most published analyses of risk associated with low penetrance susceptibility alleles, because these findings have been difficult to replicate and it is unclear how to interpret a posteriori findings from underpowered studies. It also seems specious that OEHHA characterize the conflicting findings regarding genetic susceptibility in studies of ETS and breast cancer as "diverse rather than conflicting" (response to my seventh comment on the October, 2004 draft). Whether one calls these "diverse" or "conflicting", they do not provide strong evidence in support of the hypothesis.

Response:

OEHHA has not emphasized the importance of the available data on genetic susceptibility. In the section that Dr. Thun refers to, we are simply trying to say that there are now studies providing some evidence for a gene-environment interaction and that these studies include data that shows a highly statistically significant increased risk for some individuals with specific genetic polymorphisms. We now preface that paragraph described above by Dr. Thun (section 7.4.1.4.5) with a discussion of the Surgeon General's 2004 report and IARC 2004 report and acknowledge the controversial nature of the finding of a causal association. The findings on risk modification by genetic polymorphisms are interesting, and were included for completeness. In the future, genetic polymorphisms may well explain some of the bases for inter-individual variability in response which always complicates finding effects in the general population. To clarify the above points we have changed the sentence to read "...provide <u>some</u> evidence for

gene environment interactions" as we did previously in the conclusions for active smoking.

Comment 10:

4) It can be argued that the subgroup of studies on premenopausal breast cancer deserves to be singled out, since most of these find relative risk estimates above 1.0 (Table 7.4.1.c and Figure 7.4.5). However, the data on premenopausal breast cancers derive largely from case-control studies (since breast cancer is much less common in pre- than in post-menopausal women). This downplays the evidence from the cohort studies even more than does the discussion of overall breast cancer risk. However, all of the concerns about recall bias and uncontrolled confounding, discussed above, are at least as applicable to the studies of pre- as of post-menopausal breast cancer. Furthermore, the issues of age at onset and age at exposure are separate and should not be conflated. For example, the timing of exposure is very important with respect to breast cancer risk from ionizing radiation. Women who are exposed to ionizing radiation during adolescence have a greater increase in breast cancer risk than those who are exposed at older ages. However, breast cancer is generally a "late effect" from ionizing radiation, and most of the increased risk occurs after menopause. Thus, considerations concerning age at exposure should be distinguished from issues concerning the age at onset of disease.

Response:

We do not think we have downplayed the cohort studies simply because most of the data on premenopausal breast cancers derive from case-control studies. Regarding the recall and confounding concerns, if the observed effects were the result of recall bias or confounding, one would expect similar breast cancer risk in pre- and postmenopausal women, rather than the generally higher risk observed for younger primarily premenopausal women. At least 6 of the studies that show elevated risk estimates for younger/premenopausal women (4 of which are statistically significant) report null findings within the same study for the older, postmenopausal women. It is unlikely that bias and confounding would produce an association in the younger (mostly premenopausal) but not the older (postmenopausal) women within the same studies. As well, the similarity of the summary pooled risks for cohort studies (all missing important sources of passive exposure) and the subset of case-control studies likely missing important sources of exposure, argues against recall bias or confounding as the explanation for the more elevated risks associated with the those case-control studies with more complete passive exposure assessment. Finally, the cohort studies with older age distribution will be of less use in the discussion of breast cancer risk in younger primarily premenopausal women. It should be noted that 2 of the 4 cohort studies found increased breast cancer risk in women who were premenopausal at baseline (Hirayama, 1984 and Hanaoka, 2005).

We agree that issues related to age at exposure should be separated from issues of age at onset of disease, and have not "conflated" these issues. Age-at-exposure is discussed in our document largely in the context of windows of susceptibility of mammary tissue to

transformation by chemical carcinogens; we note in that discussion the evidence that ionizing radiation exposure peri-pubertally greatly elevates risk of breast cancer. Estimation of childhood exposure thus allows exposure estimation at a window of susceptibility, and in addition, allows for more complete exposure assessment for both control and referent populations, leading to less ETS-exposed people in the referent population.

Breast cancer risk has been demonstrated to be elevated in women less than 50 years of age as a result of radiation during adolescence for lymphoma (Aisenberg et al., 1997; Bhatia et al., 1996). Thus, in contrast to what the comment implies, age-specific breast cancer rates are hugely elevated for pre-menopausal women in these studies. For example in Aisenberg et al.(1997) 8 of 33 women irradiated at less than 20 years of age developed breast cancer that was detected within 25 years of followup (making all less than 45 years of age). The RR was 56 (95% CI 23-107) for those treated at 19 years or younger. Similarly, Bhatia et al. (1996) described an estimated actuarial probability of breast cancer of 35% (95% CI 17-53%) at 40 years of age in women who had been treated with radiation peripubertally. Clearly these breast cancer risks are very elevated, and proportionately more so in younger premenopausal women as a result of early in life radiation exposure.

Comment 11:

1) Page 7-103, pp 3, line 2: Change "several" to "at least 15". Also, in line 3, insert "since the previous OEHHA report" after "studies.

Response:

Thank you, this is now changed to reflect your wording.

Comment 12:

2) Page 7-103, pp 3, line 8: Change "accounted for other risk factors" to "accounted for a number of covariates that affect breast cancer risk or diagnosis":

Response:

Thank you, this is now changed to reflect your wording.

Comment 13:

1) Pages 7-128 and 7-131: The use of a log scale for the Y axis in Figures 7.4.4 and 7.4.5 makes the results seem more similar than they are. On a log scale, small relative risks appear to be larger than they are, and disproportionately large estimates appear much closer to the others. Although this is scientifically legitimate, it exaggerates the appearance of consistency in the eyes of a general audience.

Response:

We were specifically requested by our scientific review panel to use a log scale. We had no intention of trying to manipulate the visual presentation to change appearances.

Comment 14:

2) Pages 7-129 and 7-131: Table 7.4.1.C and Figure 7.4.5 need footnotes clarifying that the Wartenberg et al. paper did not actually present results on premenopausal breast cancer) only on women less than age 50 at baseline, and that the relative risk estimates to two figures past the decimal did not come from the publication. The actual source of these should be stated.

Response:

We agree that we should have been more explicit. This has now been done in both the description of the study as well as in the footnotes for the table. The study description now states "For the purpose of developing a summary statistic at the end of this chapter, a summary risk estimate was calculated for premenopausal women using component risks and confidence intervals reported in the paper for non-smokers (combining risk ratios for current and former smoking spouses for age < 50 years; table 6). We derived cell counts from data provided in Wartenberg et al. (2000) using methods described in Greenland and Longnecker (1992) to obtain missing cell information. From cell counts we calculated a risk estimate comparing the combined exposure groups to the referent. Confidence intervals were obtained using the Woolf method described in Schlesselman (1982). Thus, for premenopausal women the derived RR is 1.15 (95% CI 0.82-1.60)." We have included a more brief explanation in the footnotes for each summary statistic that we derived and a longer explanation is now found in the description of each study.

Comment 15:

1) Page 7-132: PP 1, lines 1-4. This sentence overstates the support that "recent, population-based case control studies (as well as three cohort studies) provide for the hypothesis.

Response:

We agree and have now revised this paragraph discussing the overall breast cancer studies. As noted in response to comment 3, we have removed the word "recent", which was confusing to the reader particularly when looking at overall non-stratified results. As noted earlier, recent meant to distinguish the studies reviewed in the 1997 report from the studies reviewed for this update. The sentence has now been clarified to read: "Many population-based case-control studies (as well as three cohort studies), controlling for several important reproductive , dietary and other potential confounding factors, have identified elevated breast cancer risks for residential and occupational exposure overall or in individual strata. Higher risks were noted in some studies for breast cancer

diagnosed in women under age fifty (primarily premenopausal) or with long duration or high intensity of exposure.

Comment 16:

2) Page 7-133: The second paragraph states that "studies which include examination of peri-pubertal adolescent and prepregnancy/nulliparous exposures are preferable." This is true, provided that there is evidence that self-reports of ETS exposure in adolescence are reliable when collected in case-control studies, and that restricting the referent group to women who report no ETS exposure in adolescence is not introducing unrecognized biases.

Response:

Since both cohorts and case control studies rely on retrospective self reports of exposure in adolescence, reliable reporting is equally important for each. The issue about restricting the referent to unexposed is the same as mentioned in preceding comments. Regardless, the positive association between ETS exposure and breast cancer in younger (primarily premenopausal) women is seen in both studies that include childhood exposure and those that did not.

Comment 17:

Final comment

I believe that the disagreement between CalEPA and the great majority of breast cancer researchers can be avoided, if the report designates the evidence currently linking ETS and breast cancer as limited. This would not preclude the possibility that ETS and active smoking may affect breast cancer risk. It would not prevent CalEPA or tobacco control advocates from publicizing the issue. It would simply characterize the current information honestly and without exaggeration.

Response:

We appreciate the comments provided to us and thank the commentator for his time in reviewing the earlier draft. We do not believe we are exaggerating the available information. Rather, we believe we have done a more detailed analysis of the available studies than others who have examined the issue. Our analysis reveals a pattern of increased breast cancer risk from ETS exposure for women who are relatively young compared to older women. A number of studies have identified statistically significant elevated risk in the younger women. Furthermore, the 5 studies that did the best job of assessing lifetime exposure to ETS from all sources and excluding or limiting ETS exposed women from the referent group, obtain the highest relative risks. These risk estimates were all statistically significant for breast cancer diagnosed in younger primarily premenopausal women, ranging from 1.59-3.6, with 5 estimates being above 2. These risks are not easily explained by residual or uncontrolled confounding or bias. In addition, evidence of dose-response is seen in a number of studies. The effect is

biologically plausible as there are a number of mammary carcinogens in ETS. A number of issues raised by this commentator and others have been addressed in the latest draft which has improved the document.

References used in Responses

Aisenberg AC, Finkelstein DM, Doppke KA, Koerner FC, Boivin JF, Willet CG.(1997) High risk of breast carcinoma after irradiation of young women with hodgkin's disease. Cancer 79:1203-10.

Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows AT (1996) Breast cancer and other second neoplasms after childhood hodgkin's disease. NEJM March 21(334):745-751.

Friedman GD, Petiti DB, Bawol RD (1983). Prevalence and Correlates of Passive Smoking. Am J Public Health 73:401-405.

Greenland S, Longnecker MP (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135: 1301-9.

Howard G, Thun M (1999)Why is environmental tobacco smoke more strongly associated with coronary heart disease than Expected? A review of potential biases and experimental data. *Environ Health Perspect* 107(suppl 6):853-858.

Ruano-Ravina A, Figueiras A, Montes-Martinez A, Barros-Dios JM(2003). Dose-response relationship between tobacco and lung cancer: new findings. Eur J Cancer Prev. Aug;12(4):257-63.

Schlesselman JJ, Case-Control Studies: Design, Conduct, Analysis. Schlesselman JJ, Stolley PD. Monographs in epidemiology and biostatistics. New York: Oxford University Press; 1982; p. 176.

III.

Comment Letters Received on the Draft ETS Report on Environmental Tobacco Smoke

A. Judson Wells
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February 10, 2004

Ms. Janette Brooks, Chief
Air Quality Measures Branch
Air Resources Board
1001 I Street, P. O. Box 2815
Sacramento, CA 95812

Dear Ms. Brooks:

Enclosed are comments I would like to make re your draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003". I am sending the comments to you per instructions from Mr. Robert Krieger.

Sincerely,

A. Judson Wells

A. Judson Wells, PhD

A. Judson Wells
5 Ingleton Circle
Kennett Square, PA 19348
Phone/fax 610-388-0350

Comment on

"Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"

A draft report from the California Air Resources Board

Executive Summary

Table ES.2 on page ES-11 should include incident cases of breast cancer. The number of cases for breast cancer can be estimated by using the combined odds ratios from the two best breast cancer studies (Morabia, et al., 1996, and Johnson , et al., 2000). Their combined OR is 1.67 (95% CI, 1.29-2.16). Alternatively, one could combine the ORs from the four best studies by adding Smith, et al., 1994 and Kropp, et al., 2002. This results in an OR of 1.68 (95% CI, 1.36-2.08). However, the latter result is more heavily weighted toward younger women.

I find the range for excess lung cancer deaths from ETS in Table ES.2, 411-1,514 for California and 7,564-26,473 for the U. S. to be higher than I thought to be reasonable. On page 7.76 in the report the range is said to be 283 to 1052 deaths for California. Assuming the population of California is about 10% of the U. S. population, this would translate to about 2,830-15,200 for the U. S. The 1992 U. S. EPA report estimated lung cancer deaths from ETS exposure for the whole country at 3,000 for never smokers plus former smokers.

I also wondered if there is any way to include all causes of death from exposure to ETS, either here or in Part B. There are all cause data in Gillis et al, Eur J Respir Dis 1984;65 (suppl 133):121-126 on males, 1.04 (95% CI, 0.69-1.57), and females, 1.33 (95% CI, 0.94-1.89), in western Scotland. In the extensive data that Hirayama sent me in 1988 (referred to in the breast cancer section in B) there are also all cause data for women in Japan. The age adjusted RR is 1.17 (95% CI, 1.11-1.24). There may be other sources of all cause data. I just haven't looked. It also might be an occasion to honor G. S. Miller who is the pioneer in investigating deaths from passive smoking. In the Journal of Breathing, 1978;41:5-8, he reported that nonsmoking wives in Erie County, Pennsylvania, who were married to nonsmokers lived 4 years longer (78.8 versus 74.7) than wives married to smokers. This was 2+ years before the 1981 reports of Hirayama and Trichopoulos on ETS and lung cancer.

Part A

Pages III-4 and 5. There has been too little attention paid in the U. S. to the work of Pritchard et al, Environ Technol Lett 1988;9:545-552, at Harwell in England on what

happens to aged, diluted ETS. They labeled tobacco smoke with a radioactive isotope of iodine in 1-iodohexadecane, which boils at 380 degrees C., about in the middle of the boiling point of tobacco tar. They used a 14.4 m^3 chamber and found that, during aging and dilution, 70% of the particulate ETS tar evaporates into the vapor phase. Vapor phase tar, like other organic vapors (Bond et al, Toxicol Appl Pharmacol 1985;78:259-267) would deposit quantitatively in the lung, and the lung has no clearance mechanism for vapor phase deposits, whereas only about 15% of the particulates deposit in the lung, the remainder being exhaled. This phenomenon could go a long way toward explaining why the passive risk is so similar to the active risk in non-contact sites like the heart and breast. It appears that the tar compounds that would evaporate would have molecular weights in the 100 to 200 range which would include quinoline, ethyl quinoline, benzoquinoline, phenanthridene, nornicotine, beta-naphthyl amine, nitroso pyrolidine, nitroso nornicotine, pyrene, fluoranthene, phenol, the cresols, 2,4-dimethyl phenol, catechol, and the methyl catechols, all of which have some carcinogenic activity.

Part B

On page 4-6 in the discussion of McMartin et al., 2002 there is no mention of the significance of higher nicotine in the SIDS babies, but not higher cotinine. This means that the relevant exposure occurred during a very short time before the death occurred, namely, during the half-life of nicotine.

In Chapter 6 there is no mention of Chronic Obstructive Lung Disease (COLD) as an outcome of ETS exposure. I know of two such reports. Kalandidi et al. Lancet, 1987;Dec 5:1325-26, found that never smoking wives married to smokers had incidence ORs of 1.3 (95% CI, 0.7-2.3) with exposure to less than 300,000 husband's cigarettes in their lifetime, and 1.7 (95% CI, 0.8-3.4) for exposure to more than 300,000 cigarettes, versus wives married to nonsmokers. Hirayama, in the 1988 personal communication referred to above, found an age adjusted RR of 1.32 (95% CI, 0.8-2.1) for death from emphysema or bronchitis when his Japanese wives were married to a smoker vs. a nonsmoker. There may be other references, but I haven't looked.

In Chapter 7, Table 7.0B there is no mention of radioactive polonium which I remember as a component of ETS, and which I believe is carcinogenic. On page 7-10 the reference to the EPA report as Wells (1992) could be more specific by listing it as (Wells, 1992b) and referencing it as Wells AJ (1992b), In: U.S. EPA (1992) Respiratory Health .....Washington, DC., Appendix B. Reference1992a should be reserved for my 1992 letter in Am J Epidemiol, which goes with the 1991 letter in AJE. You will probably be criticized if you don't refer to the work of tobacco consultant Peter Lee, who still doesn't agree that misclassification of smokers as nonsmokers is a small effect.

On page 7-12 the 1997 report missed the all cancer passive smoking data in Gillis et al., Eur J Respir Dis 1984;65 (suppl 133):121-126. They report on 44 male cancer deaths and 144 female cancer deaths. In my 1988 paper in Environment International, Wells AJ (1988), Environ Int 1988;14:249-265, the risks from cancers other than lung

(five studies) and lung cancer are reported separately, but they are easily combined to get total cancer results. My paper in J Women's Cancer 2000;2(2):55-66, Table 1, also gives a total cancer risk of 1.4 (95% CI, 1.1-1.8) by combining the results from various studies.

On page 7-67 mention should be made about the errors in underlying studies of lung cancer from workplace ETS exposure, specifically Wells AJ et al., J Natl Cancer Inst 1997;89:821-822 on errors in Garfinkel et al (1985), and Wells (1998b) on errors in Janerich, et al., (1990). On page 7-74 the meta-analysis in Wells 1998b of 15 studies, RR = 1.19 (95% CI, 1.07-1.34), should be added to the list in the first paragraph even though it covers only workplace exposure.

On page 7-93 the statement that Millikan's ORs for current smoking are versus never active/passive of 1.0 (0.7-1.4) and following is wrong. Those ORs in their Table 2 are versus all never smokers, except for the ETS result at the bottom of the table. At the top of page 7-94 the "limitations" should include not using non-ETS exposed never smokers in the referent for the main OR's as well as the age 18+ referent for the passive smoking OR.

On page 7-97, Marcus et al., I would add "all" to the last word in line 6. Also it should be noted that the ETS results in their Table 2 are for smokers as well as nonsmokers.

On page 7-101 there is a reference to Wells, 2002 (should be 2003), but this reference does not appear in the reference list on page 7-203. The reference is Wells AJ. Breast cancer and tobacco smoke [letter]. Br J Cancer 2003;89:955.

On page 7-102, last line, add "all" to never-smokers. The 1.60 RR on the next page is probably crude. The adjusted RR in Table II is 1.61 (95% CI, 1.19-2.19). It would also be worth including their RR for exposure for 40+ years and 20+ cigarettes per day of 1.83 (95% CI, 1.29-2.61).

On page 7-104, another weakness of the Band et al., study is that they did not consider using non-ETS exposed never-smokers as their referent.

On page 7-103 under Terry, et al., 2002a, mention should be made of their observation that 40+ cigarettes per day yields a RR of 1.34 (95% CI, 1.06-1.69) and that 40+ years and 20+ cigarettes per day yields 1.83 (95% CI, 1.29-2.61). Also Terry, et al., should be included in Table 7.4B. Mention in the active smoking section might be made of Couch, et al., Cancer Epidemiol Biomark Prev 2001;10:327-332, that women with a family history of three or more cases of breast or ovarian cancer had a breast cancer RR of 2.4 (95% CI, 1.2-5.1) for ever smokers relative to never smokers. Also Manjer, et al., Int J Cancer 2001;91:580-584, report that women with estrogen receptor-negative breast tumors have RRs of 2.21 (95% CI, 1.23-3.96) for current smokers and 2.67 (95% CI, 1.41-5.06) for former smokers, relative to women who have never smoked. I believe

there is other evidence that women with estrogen-negative tumors are at higher risk from tobacco smoke.

In Table 7.4B there is no referent shown for Lash and Aschengrau (1999), Kropp and Chang-Claude (2002), or Lash and Aschengrau (2002). In Table 7.4C on page 7-118 there is no referent shown for Morabia et al. (2000) These should all be "No active/passive". Also I have a letter from Sarah Smith in which she says, referring to their paper, Smith et al., (1994), that ever smokers not exposed to other's ETS had an OR of 2.00 (95% CI, 0.98-4.12) compared with non-ETS exposed never smokers. This information was published in Wells (1998b).

In pages 7-119 and following the reference Wells (1998) should be changed to Wells (1998b). On pages 7-120 and 7-121 re the Smith et al., (1994) paper the risks shown were taken from their Table IV, which is for smokers and nonsmokers exposed to ETS. Even though there is less statistical significance in individual categories because of the smaller numbers, I think CalEPA ought to go with the numbers in Smith's Table V for the effects of ETS exposure on never smokers only. Throughout the literature the passive smoking risk that is sought is that for ETS-exposed never smokers relative to non-ETS exposed never smokers. One could set up separate studies of the effect of ETS exposure on smokers, but the two should never be combined. The high statistical significance that you show for lifetime exposure based on Table V in Smith, et al., 2.53 (95% CI, 1.19-5.36) is good enough. The whole paragraph should be rewritten.

On page 7-122 there is a reference to Terry et al., 2002. There are two Terry 2002 references in the reference list, page 7-202. Here you probably mean 2002b since there are no passive smoking data in 2002a. Also on page 7-122 there is no mention of Zhao et al., Matched case control study for detecting risk factors of breast cancer in women living in Chengdu (in Chinese). Chung Hua Liu Hsing Ping Hsueh Tsa Chih (Clin J Epidemiol, probably for China) 1999;20:91-94, nor of Lui et al., Passive smoking and other factors at different periods of life and breast cancer risk in Chinese women who have never smoked – a case control study in Chongqing, People's Republic of China. Asian Pacific J Cancer Prev 2000;1:131-137, both of which contain data on passive smoking and breast cancer as indicated in Table 7.4E, but there are no explanatory paragraphs for them in pages 7-123 to 7-131, nor are they included in the reference list, pp 7-198, 7-204.

The best thing to do with Marcus et al, (2000) pages 7-126 and 127, is to omit it from the passive smoking part of the report. There are no good passive smoking data in it. All of the exposed groups include smokers as well as never smokers. See discussion above under Smith et al. In the OR where the referent is "no exposure and no history of active smoking" the smokers were eliminated in the referent, but, based on the cell counts, the smokers are still included in the exposed group.

Under Morabia, et al., (2000 and 1998) on page 7-127, would it be helpful to refer to Figure 7.4.3 toward the end of the first paragraph. Under Wartenberg, et al., (2000) at the top of page 7-129, the wording could be a little more definite. Try "Nevertheless,

since the ETS exposures other than from spouse were included in the questionnaire only at one point in time, namely, at enrollment, The potential for...." Under Nishino, et al., (2001) page 7-129, mention should be made of their statement on page 801 of their paper that "women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoking exposure".

On page 7-132, under Khuder and Simon, there is an error in the paper. From their Table 2 the actual ORs for the lowest levels of exposure range from 0.80 (Wartenberg) to 3.10 (Morabia), and for highest levels, from 1.10 (Warternberg) to 3.20 (Morabia). K & S is a very sloppy paper. For example they include Marcus, et al., in the dose response list with only one value. Also the RR for Wartenberg in Table 1 is wrong.

On page 7-135, Table 7.4D, a footnote on what the IARC classifications mean would be helpful. Also why are Delfino, et al., Egan, etal., and Wartenbeg, et al., excluded from Figure 7.4.2? On page 7-137, Nishino, et al., is also a new prospective study. Jee, et al., has dose response, 1.2, 1.3, and 1.7. Both Lui, et al., 2000 and Zhao, et al., 1999 are listed on page 7-137, but the are no descriptions of these studies in the earlier text, nor are they listed in the reference list on pages 7-198 and 7-204. Why is Millikan, et al., missing from Table 7.4E? Why is Kropp, et al., labeled "likely" in Table 7.4E and "unlikely" in Table 7.4F? Also Hirayama and Jee are "unlikely " in Table 7.4E and "likely" in Table 7.4F. On page 7-140 it is stated that there are 15 studies. Actually there are 16 studies; Millikan is missing from Table 7.4E and Lui from Table 7.4F, Figure 7.4.4 and Table 7.4G.

In Table 7.4I, page 7-149, under Delfino, et al., isn't it better to use their low risk controls (60 cases) yielding a passive OR of 1.78 (95% CI, 0.77-4.11). In Table 7.4J there is no referent shown for Lash, et al., 1999, 40/139, or for Lash, et al., 2002, 80/53.

I find Tables 7-4I and 7.4J confusing. If Table 7.4I is supposed to include all of the case-control studies, it is missing Morabia, Smith, Liu, Sandler, Zhao, and Lash 2002. As noted above, I would omit Marcus. If Table 7.4J is supposed to include the case-control studies with dose-response, it is missing Morabia, Smith (child only, adult only, child plus adult) and Liu. On page 7-154, Table 7.4L, Hirayama and Nishino are missing. Also the word "Deaths" in the heading for Cases should be removed in both Tables 7.4L and 7.4M because some of the cohort studies used diagnosis. In Jee, the RR for wives exposed to current smokers for more than 30 years (1.7, 95% CI, 1.0-2.8) should be added to both Tables 7.4L and 7.4M.

In the reference list on page 7-203, Wells AJ 1991, 1992a, 1998a, and 2001 should be designated as letters. Also there is an Erratum associated with 1998a, which is noted at Am J Epidemiol 1998;148(3):314.

As a general comment on ETS and breast cancer, I know that your general plan is to discuss active smoking first, then passive smoking, and finally biological plausibility. This makes sense for lung cancer, but for breast cancer the reverse may be better. Start with the exposure windows, probable hormonal effects, and animal studies of breast specific carcinogens. Then get into passive smoking, and finally into active smoking. The advantage of this order is that it explains why the active smoking effect depends so much on the referent that is used, either including or excluding passively exposed never smokers, and it leads to an explanation of why the passive effect is almost as large as the active effect.

In Chapter 8, Table 8.1, page 8-3, and in the text on pages 8-10 and following, the comments on Wells (1998) are restricted to workplace exposure only. Actually there is an Appendix in that paper which updates Wells' 1994 meta-analysis (J Am Coll Cardiol 1994;24:546-554). The update includes 19 studies that were available at that time, and breaks the results down by morbidity and mortality, males, females and both genders, four quality tiers, and exposure from spouse only, home only, and all adult exposures. The quality tiers were taken from my 1994 meta-analysis (above) and were based on the number and importance of the other risk factors that were adjusted for. The combined RR for morbidity for tier 1, the top quality tier, and all adult exposures for males plus females is 1.86 (95% CI, 1.20-2.88). For all home exposures only, the combined RR is 1.63 (95% CI, 1.22-2.18), and for spouse exposure only, it is 1.39 (95% CI, 1.06-1.82). This demonstrates that better questionnaires lead to higher RRs, and that the real relative risk may be nearer 1.8 than 1.25. For mortality, tier 1, males and females combined, the RR for all adult exposures is 1.87 (95% CI, 0.56-6.20), but for many fewer cases. For spouse exposure only for mortality for all studies combined, the RR is 1.21 (95% CI, 1.09-1.35), in reasonable agreement with the other meta-analyses, but less than the 1.8 from the better studies.

On page 8-6, Table 8.1 under Raitakari, et al., it looks like ETS in the third column needs to be lowered one line. On pages 8-16/17 I could find no reference in the description of You, et al., to Figure 8.03. On pages 8-32/33/35 on platelet effects and animal studies there is no mention of the rather thorough discussions on these subjects in the 1997 report. Even with a mention of those discussions, you may want to refer to some of that work. I am thinking particularly about the work of Burghuber, et al., and Davis, et al., on platelets, Zhu, et al., on rabbits, and Penn, et al., on cockerels.

All in all it is a very good report.

A. Judson Wells

A. Judson Wells, PhD

City and County of San Francisco
Department of Public Health
Population Health and Prevention

TOBACCO FREE PROJECT
Community Health Education Section
Community Health Promotion & Prevention Branch

April 9, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
1001 I Street / P.O. Box 2815
Sacramento, California 95812

Re: Environmental Tobacco Smoke

Dear Ms. Brooks,

This letter is to provide comment on the Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant issued by the Air Resources Board in December of 2003. As the Tobacco Free Project Director for the San Francisco Department of Public Health, I support the above report as it provides documentation of environmental smoke as a toxic air contaminant. In addition to providing data on exposure both in indoor and outdoor settings, the report documents the multitude of health effects from the toxic air contaminant environmental tobacco smoke.

My office receives complaints about smoking in the workplace, which we refer for enforcement, as well as complaints about smoking in multi unit housing sites. Many of the complainants are particularly susceptible to the hazards of environmental tobacco smoke due to asthma and other respiratory conditions. Unfortunately, the remedies for those who are being exposed to environmental tobacco smoke in their homes due to neighbors smoking are limited. While the classification of environmental tobacco smoke as a Class A carcinogen by the Environmental Protection Agency provided invaluable support for the adoption of protection from this toxic air contaminant in the workplace, I believe that the Air Resources Board report can also provide support for the development of additional protections from exposure in other settings. I understand that if the Air Resources Board identifies environmental tobacco smoke as a toxic air contaminant, it will be listed in Title 17 of the California Code of Regulations under section 93000. Should this occur, I also understand that the law requires the Air Resources Board to prepare a report, which assesses the need, and appropriate degree of control of a toxic air contaminant, in consultation with the local districts, affected industry, and the public. Additional control of this toxic air contaminant would be very valuable for the protection of public health, as it would provide an additional tool to reduce exposure to a known carcinogen and toxic air contaminant.

Thank you for the opportunity to provide public comment on this important public health issue.

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March 25, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
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RE: Draft Technical Support Document for the Proposed Identification of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (December 2003)

Dear Ms. Brooks:

Lorillard Tobacco Company submits the following comments in response to the California Air Resources Board (CARB) Draft Technical Support Document for ETS (Draft Report). As explained in these comments, the available scientific evidence does not support the conclusions presented in Part A of the Draft Report regarding the adverse health effects of ETS, and the exposure assessment in Part B of the Draft Report provides an inadequate basis to list ETS as a Toxic Air Contaminant (TAC).

I. THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT'S (OEHHA'S) CONCLUSIONS REGARDING THE ADVERSE HEALTH EFFECTS OF ETS ARE NOT SUPPORTED BY THE AVAILABLE SCIENTIFIC EVIDENCE

OEHHA acknowledges that its analysis of the health effects of ETS in Part A of the Draft Report rests largely on the 1997 OEHHA Report: "Health Effects of Exposure to Environmental Tobacco Smoke". The tobacco industry submitted extensive comments on the 1997 OEHHA

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Report. Those comments pointed out major deficiencies in the OEHHA scientific analysis and ETS risk assessment, including OEHHA's failure independently to evaluate the scientific record; failure to employ objective, scientifically sound criteria; failure to follow accepted risk assessment procedures, including those recommended by federal EPA and California EPA Advisory Committee; and selective reliance on weak, inconsistent and unreliable studies.

The deficiencies in the 1997 OEHHA ETS Report have not been corrected, and the tobacco industry's comments on the 1997 Report remain valid. Moreover, contrary to the assertions in Part A of the Draft ARB Report, scientific studies published since 1997 weaken, rather than strengthen, OEHHA's 1997 conclusions with respect to the health effects of ETS. This is explained and documented in the attached comments from J. Daniel Heck, Ph.D., et al., and in comments submitted for the record by Maurice LeVois, Ph.D.

II. THE ARB EXPOSURE ASSESSMENT PROVIDES AN INADEQUATE BASIS TO LIST ETS AS A TAC

A. The ARB's Authority is Limited to Outdoor Air

Under the Tanner Act, passed in 1983, the ARB has authority to identify and adopt control measures for "toxic air contaminants" (TACs). The ARB's authority to regulate TACs is limited to ambient or outdoor air. The ARB has no authority to regulate indoor air or to rely upon indoor air exposure as a basis for regulation of outdoor air. The ARB's authority extends only to those substances emitted into the "ambient air". The term "ambient air" encompasses only outdoor, not indoor, air. Health & Safety Code, § 39657 ("the state board shall identify toxic air contaminants which are emitted into the ambient air of the state"); *see also*

Health & Safety Code § 39660 (the ARB shall evaluate the health effects of and prepare recommendations regarding substances . . . which may be or are emitted into the ambient air of California and which may be determined to be toxic air contaminants"); Health & Safety Code, § 39013 ("'Air contaminant' or 'air pollutant' means any discharge, release or other propagation into the atmosphere"); 40 C.F.R. § 50.1 (interpreting the Clean Air Act and defining "ambient air" as "that portion of the atmosphere, external to buildings, to which the general public has access"). The limitation of the ARB's authority to outdoor air is confirmed by the fact that the ARB has not previously sought to identify or regulate any TAC in indoor air, or to rely upon indoor exposure as a basis to identify or regulate a TAC in outdoor air.

California Health and Safety Code Section 39660.5 provides that "[i]n evaluating the level of potential human exposure to toxic air contaminants, the state board shall assess that exposure in indoor environments as well as in ambient air conditions". The law further provides that, when the state board identifies toxic air pollutants that have been found in any indoor environment, the state board shall refer all available data on that exposure and the suspected source of the pollutant to identified state agencies with regulatory responsibility over indoor air. This provision makes clear that, while the ARB is obligated to assess exposure in indoor environments, it has no regulatory power over indoor air, and it must refer its assessment of indoor air exposures to those agencies that have regulatory responsibility for such exposures. Because the ARB has no regulatory responsibility for indoor air, it cannot rely upon indoor exposure levels as a basis to identify or regulate a TAC.

B. **The Draft Exposure Assessment Does Not Demonstrate a Meaningful Level of Outdoor ETS Exposure**

The ARB acknowledges that "ETS emissions and exposure are very localized" and "only very limited data on outdoor ETS levels are available." (p.V. 1). In view of the limited data on outdoor ETS exposures and the localized nature of such exposures, the ARB lacks a reliable scientific basis to conclude that ETS exposures in the outdoor environment in California are of sufficient intensity, duration or scope to justify listing ETS as a TAC.

The ARB has made no effort to determine the number of people exposed to ETS in the ambient air in California, or the level or frequency of such exposure, and no data is cited in the Exposure Chapter from which such determinations can be made. In the absence of such data, there is no sound scientific basis to list ETS as a TAC.

The ARB's ETS exposure evaluation is inconsistent with the U.S. EPA's Final Guidelines for Exposure Assessment (EPA 1992). The EPA Guidelines provide that an exposure assessment should describe the intensity, frequency and duration of contact with the substance under review (Section 2), that personal monitoring is the preferred method of exposure measurement (Section 2.2.1), that time of contact should be accurately characterized by demographic data, survey statistics, behavior observation, or the like (Section 2.2.2), and that it is important to link the time an individual is in contact with a chemical to the concentration of the chemical to which the individual is exposed (Section 4.3). As noted, the ARB exposure assessment fails to satisfy any of these criteria. The ARB has not calculated, or provided a reliable basis to estimate, either the concentration, frequency or duration of ETS exposure in the

outdoor air; nor has it estimated the number of people potentially exposed to ETS in the ambient air in California.

1. The Rogge Study is Flawed and Outdated

The exposure Chapter cites a study by Rogge, et al. (1994) that attempted to estimate concentrations of fine cigarette smoke particles in the Los Angeles outdoor air. The Rogge study is outdated and fundamentally flawed. First, the Rogge study was based on fine particulate matter samples collected in the Los Angles area in 1982. The ARB acknowledges that California smoking rates have declined significantly in the ensuing 22 years. Consequently, the Rogge study is out of date and of little relevance to current exposure patterns.

Second, the Rogge study contains numerous serious flaws. The Rogge paper's abstract states that the authors have estimated that 1.0 - 1.3% of Los Angeles outdoor air fine particulates are derived from ETS. However, this estimate is more correctly described on the last page of the published paper as the maximum possible ETS-apportioned contribution. The Rogge report employed an emissions factor of 20.4 mg fine particulate matter per cigarette, a value obtained from the prior 1991 study of Hildemann *et al.* (Rogge reference #20). This value is nearly twice the 13.3 mg/RSP/cigarette emissions factor employed elsewhere in the ARB draft. (Table B-2.)

The Rogge study employed eleven 2- and 3-methyl substituted alkenes identified in airborne particulate samples to develop the source apportionment calculations. The authors referenced prior work to support a statement that a characteristic quantitative relationship among three of these marker compounds is unique to tobacco smoke and may be used to identify the ETS contribution to outdoor urban air fine (<2 um) particulate material. The authors state that

the three selected marker compounds are not derived from other green or dry plant sources in the local environment, but a full accounting for additional alternate sources is not presented. The authors' implicit assumption that ETS is the sole source of the markers employed in the source apportionment calculations is therefore tenuous. Nor is there any explanation for the fact that utilization of any of several of the other eight marker compounds reportedly found in cigarette smoke produces substantially lower estimates of the contribution of ETS to total outdoor particulates. Several of those estimates are zero or very near to zero, depending upon which combination of marker compound and sampling location is considered from the published report.

No explanation is offered for the differences in the ratios of the eleven cigarette smoke constituent compounds, including the three assumed "ETS-specific" marker compounds, between cigarette smoke and the outdoor air samples. These differences are even more dramatic for several of the less abundant marker compounds; several of these were not detected in some of the urban air particulate samples.

A detailed critique of the Rogge study is attached to these comments as Appendix A.

2. Personal Monitoring Studies Provide the Most Reliable Basis for Measuring ETS Exposure

It is well established that personal monitoring studies provide a more reliable and highly preferred method for measuring inhalation exposures to ETS or to other airborne substances as compared to area monitoring studies. (Jenkins, *et al.*, 1991, Sexton, *et al.*, 2004; NIOSH). Personal monitoring studies accurately measure both components of exposure, duration and concentration. Area monitoring studies provide no data on duration of exposure

and do not accurately measure exposure concentrations in the breathing zones of particular individuals. The ARB draft largely ignores the findings of the Oak Ridge study of personal monitoring of ETS in 16 U.S. cities (Jenkins, Polausky and Counts, 1996). This large, well controlled investigation of nonsmokers' actual breathing-zone exposures to ETS in the home and outside of the home included measures of a number of ETS markers. The ARB presents no justification for ignoring these findings.

The Eisner study (2001) is the only personal monitoring study cited in the Exposure Chapter that includes measurements of ETS exposure in the outdoor air. The Eisner study employed personal badge-type passive nicotine monitors worn for 7 days. The 18 study subjects reporting outdoor ETS exposure only had a median nicotine exposure in outdoor air of 0.025 ug/m 3. In fact, seven of 18 subjects (39%) had no detectable outdoor nicotine exposure, despite having reported such exposures during the 7 day monitoring period. This study suggests that the ARB's exposure scenarios are highly unrealistic and provides strong evidence that there is insufficient outdoor air exposure to justify regulating ETS as a TAC.

3. The 2003 ARB Air Monitoring Study Is an Inadequate Basis to Calculate Outdoor ETS Exposures

The ETS outdoor exposure levels calculated in the Exposure Chapter are based exclusively on a 2003 ARB air monitoring study. In this study, nicotine measurements were taken over a 3 day period in five outdoor smoking areas, near an airport, community college, amusement park and two office buildings. This study does not provide a reliable basis to calculate outdoor ETS exposures, for the following reasons:

a) There are serious technical problems with the monitoring study. The Field Spikes and Trip Spikes were apparently prepared at only one level per field nicotine sample set, with reported fortifications of 400 ug (airport samples), 100 ug (community college samples), 50 ug (office building #1 samples), 25 ug (office building #2 samples), and 10 ug (amusement park samples). Nicotine recoveries for the Field Spike samples reportedly ranged from 76% to 89%; Trip Spike nicotine recoveries were similar, 72% to 89%. However, the levels of nicotine fortification employed in the spike samples appear to have been generally tens, hundreds or thousands of times higher than those reported for the actual field samples of nicotine collected in the various ETS environments. Therefore, the spike sample controls employed to evaluate the accuracy of the field sampling, handling, extraction and quantification procedures are entirely inappropriate for the actual reported levels of outdoor air nicotine, as they span a range of nicotine vapor concentrations that are well above those measured.

Standard, validated methods for the collection and measurement of ETS-derived nicotine and particulate material are readily available, as are methods for other ETS marker analytes having advantages over nicotine (CORESTA Recommended Methods 50, 51, 52; ASTM-D 5075-96 Standard test method for nicotine and 3-ethenylpyridine in indoor air; ASTM D 5955-96 Standard test method for estimating ETS contribution to respirable suspended particles based on UVPM and

FPM; ASTM D 6271-98 Standard test method for estimating ETS contribution to respirable suspended particles based on solanesol.)

b) Only a few, unrepresentative outdoor venues were chosen for monitoring. These sites appear to have been selected arbitrarily, or to represent maximum potential exposures, rather than under any science-based protocol designed to assure representativeness.

c) Monitoring was conducted only in, or immediately downwind and adjacent to, designated smoking areas, which can be readily avoided by non-smokers and, thus, are not representative of typical ETS exposures in the ambient air.

d) The ARB study was an area monitoring study that did not measure exposure duration or the level of exposure to particular individuals. Contemporary standards for exposure assessments include a strong preference for personal monitoring data over area sampling (NIOSH).

e) The ARB study used nicotine as the marker for ETS exposure. There are well established and significant shortcomings to the use of nicotine as an ETS marker. (Nelson, *et al.*, 1992). The ratio of nicotine to smoke particulate or gas phase constituents that may be of interest to human health has long been known to vary significantly over time and under different ventilation conditions in indoor ETS field studies. The instantaneous and effectively infinite dilution of ETS emitted into outdoor air, combined with the likelihood of nicotine absorption to any number

of outdoor environmental surfaces in the proximity of smokers, renders risk estimation of outdoor exposures based upon nicotine levels even more problematic than it is in the indoor environments that have been the subject of extensive prior investigation.

The abundantly documented shortcomings of ETS nicotine as a marker for other ETS constituent levels largely derive from its distinct and characteristic decay kinetics and complex absorption/desorption behaviors on environmental surfaces [Jenkins, 2000 #2012]. The CARB draft report mentions these briefly and includes some (but far from all) relevant citations to this literature. The report acknowledges on Page V-6 that " . . .3-EP is better than nicotine as a marker for vapor phase ETS . . . " but then goes on to cite a 'personal communication' from a CARB staffer (Poore, 2002) and LaKind, et al., (1999) in support of the listed shortcomings of 3-EP relative to nicotine.

However, an examination of the LaKind, et. al., paper reveals that CARB has taken a sentence out of context to imply that the authors endorse the use of nicotine over 3-EP as a preferred marker for ETS, which is incorrect. The LaKind paper discusses the relative merits and shortcomings of all of the available ETS particulate and vapor phase markers. The section of the LaKind paper to which the CARB draft refers was in fact a discussion of a number of reasons that 3-EP is preferred over nicotine, and not the other way around, as the CARB draft implies.

Notably, 3-EP is present in ETS at nearly the same levels as nicotine, it exhibits first order decay kinetics and is more stable to UV irradiation than nicotine. CARB should rephrase this section to accurately reflect the peer-reviewed conclusions and opinions in the LaKind paper.

f) In virtually all previous TAC exposure assessments, the ARB relied upon California population-weighted exposures to outdoor average ambient concentrations of the candidate substance. For ETS, by contrast, the ARB has relied exclusively upon localized short term exposures in, or immediately downwind and adjacent to, designated smoking areas, data that have no relevance to general long term ETS exposure in the ambient air in California.

g) The ARB air monitoring study has not been published in a peer-reviewed scientific journal.

4. The ARB's Scenario-based Approach Is an Inadequate Basis to Demonstrate Outdoor Exposure to ETS

The Exposure Chapter presents several hypothetical children and adult ETS exposure scenarios to estimate public exposure to ETS in the outdoor environment. This is an unprecedented and unreliable method for calculating outdoor exposure. The ARB exposure scenarios are not based on activity pattern studies or other empirical evidence. Rather, they are based on unverified, arbitrary and exaggerated exposure assumptions. In particular, the assumptions with respect to children's outdoor exposures are highly unrealistic. For example, the critical assumption that children play outdoors in an area that is adjacent to a neighboring

business smoking area is highly implausible. The ARB exposure "Scenario T2: Business Traveler Exposure - Bar", described on pages V-46 and V-47, includes a creative but speculative exposure of 1 hour in a California bar that does not comply with the California work place smoking prohibition. Current survey data on the rate of compliance with California's smoking ban should be included to provide a perspective on the likelihood of this hypothetical exposure. This fanciful hour-long exposure to indoor air having 31.1 ug/m^3 nicotine exposure accounts for fully 97% of the total exposure for this scenario, and in any event is irrelevant to the CARB charge to regulate outdoor air, not indoor air.

The T2 scenario also includes a hypothetical hour-long meal in an outdoor restaurant, "very near the smoking area of a nearby office building" that results in an exposure to 0.19 ug/m3 nicotine, identical to that reported for the "Office Building #2" sampling site. The ARB should address the likelihood that ETS could conceivably travel from such a smoking area to any "very near" outdoor space without any further dissipation or dilution.

The U.S. EPA's Final Guidelines for Exposure Assessment (EPA 1992) provide criteria for the proper development of scenario - based exposure estimates (Section 5.3.3). The ETS exposure scenarios included in the ARB draft report do not satisfy the EPA standards and do not provide a sound basis for regulation of ETS in outdoor air. The EPA Guidelines provide that a proper exposure scenario should include:

- The characterization of the chemical, i.e., amounts, locations, time variation of concentrations, source strength, environmental pathways from source to exposed individuals, fate of the chemical in the environment, etc. (characterization of the chemical)

- Identification of the individual(s) or population(s) exposed, and the profile of contact with the chemical based on behavior, location as a function of time, characteristics of the individuals, etc. (characterization of the exposed population)

- As noted, the ARB has failed adequately to characterize the intensity, duration or frequency of ETS exposure in outdoor air, and failed properly to characterize the exposed population.

Even under the exaggerated outdoor ETS exposure scenarios posited by ARB, indoor air accounts for 89-99% of total hypothetical ETS exposure to children and adults. (Table V-11.) The very small contribution of outdoor exposures to total ETS exposures does not justify the extraordinary step of regulating ETS as a TAC.

5. **Uptake/Biomarker Data from Experimental ETS Exposures is Available and Should be Considered and Discussed by the ARB**

The laboratory study of Scherer and colleagues (G. Scherer, C. Conze, A.R. Tricker and F. Adlkofer (1992) *Clin. Investig.* 70:352-367) comprises a controlled human clinical exposure to extremely high levels of ETS with assessment of a variety of sensitive biomarkers (urinary mutagenicity, PAH metabolites, DNA adducts). This investigation found no significant elevations in the measured endpoints at levels of ETS exposure far above any that could conceivably result from the outdoor air exposures posited by ARB. The ARB should include discussion of this and other available scientific information in regard to the biological plausibility that a measurable risk to Californians could conceivably result from outdoor ETS exposures.

C. All Prior TAC Listings Have Been Based On More Extensive and Reliable Exposure Data than That Available For ETS

The ARB's Draft Report does not identify the number of people exposed to ETS in the ambient air in California, or the duration or level of such exposure. By contrast, in all other listing recommendations, the ARB has relied upon statewide population-weighted background exposure levels or comparable data. In the few cases in which a statewide number was not available, the ARB's listing recommendation has included an average continuous exposure level for particular air districts or exposure levels for a significant subset of the population residing near a particular emissions "hot spot." This exposure data is generally compiled from samples collected from California's 20 station toxic monitoring network, or district or source specific monitoring conducted over time. In previous listing recommendations, such data demonstrate that large portions of California's population is exposed to the substance in question on a continuous basis. For example, in previous TAC listings, the ARB offered the following exposure estimates:

- Acetaldehyde - estimated statewide population-weighted exposure of 2.33 parts per billion based on exposure to 20 million people in California.
- Benzene - a South Coast Air Basin population-weighted year round average of 4.6 parts per billion.
- Benzo[a]pyrene - statewide population-weighted exposure of 0.53 nanograms per cubic meter based on exposure of 20 million people in California.

- Butadiene - statewide population-weighted exposure to outdoor airborne butadiene, based on data from the ARB's toxic monitoring network, estimated to be an average of 0.37 ppbv or 0.82 micrograms per cubic meter.
- Cadmium - 10 million people exposed to an average cadmium concentration of 1.0 to 2.5 ng/m^3 and one million people exposed to an average cadmium concentration of 1.8 to 5.6 ng/m^3.
- Carbon Tetrachloride - toxic monitoring network results yielded a statewide annual average concentration of 0.13 parts per billion.
- Chloroform - routine monitoring at 19 sites yielded an estimated statewide population-weighted exposure of 0.03 ppb.
- Diesel emissions - based on emissions inventory projections, staff estimated that statewide population-weighted outdoor diesel exhaust PM_{10} concentrations were 1.8 ug/m^3 for 2000 and 1.7 ug/m^3 in 2010.
- Ethylene dibromide - ambient concentrations for the South Coast Air Basin were .0074 ppb (average annual) and .004-.18 ppb (24 hour).
- Formaldehyde - overall mean statewide exposure, weighted by population, estimated to be 4.4 ppbv.
- Inorganic arsenic - approximately 20.3 million people in California were estimated to be exposed to a population-weighted mean inorganic arsenic outdoor air concentration of 1.9 nanograms per cubic meter.

- Methylene chloride - approximately 20.3 million people (80 percent of the state's population) estimated to be exposed to a population-weighted mean concentrations of 1.1 to 2.4 ppb.
- Nickel - estimated mean statewide population-weighted exposure to nickel for the 20.3 million people represented by the ARB's monitoring network was 7.3 nanograms per cubic meter.
- Perchloroethylene - estimated average population-weighted exposure for approximately 20 million Californians residing in the combined areas monitored by the 19 stations was 0.37 ppbv.
- Trichloroethylene - approximately 20 million people in California represented by the toxics air monitoring network estimated to be exposed to a population weighted mean concentration of 0.22 ppb.

Unlike the substances discussed above, the ARB is unable to provide any estimate of the percentage of Californians exposed to ETS in the outdoor air, the levels at which such exposure occurs, or the time period over which such exposure continues. The ARB's Draft indicates at ES-6 that "[i]nformation from several smoking behavior related surveys indicate that California's adults, adolescents, and children are exposed to ETS during some time of the day. According to studies from the late 1980's and the early 1990's, on a given day, 56% of adults, 64% of adolescents and 38% of children may be exposed to ETS during their daily activity." However, the Draft Report provides no indication of how many people are exposed to ETS on a daily basis, at what levels they are exposed, for what period of time they are exposed and whether or not such exposure occurs indoors or outdoors. Further, this statement is based on

studies conducted over ten years ago, and has little bearing on current ETS exposure levels. Unlike in previous cases, the ARB has not measured, and does not have sufficient information to estimate, "background" exposure levels to outdoor ETS. The only studies of outdoor ETS cited by the ARB are two published studies attempting to measure outdoor air concentrations of ETS outside of California, and a recent study collecting limited samples in a small number of outdoor smoking areas in California. ES - 6. The ARB does not suggest that such limited information is a reliable or sufficient basis upon which to base a general estimate of statewide exposure levels, or even an estimate of how many Californians might be exposed to ETS at some level in the outdoor environment.

D. OEHHA Failed to Calculate a Health Risk from Outdoor ETS Exposure

The Tanner Act requires OEHHA to evaluate the levels of outdoor exposure to a potential TAC that may cause or contribute to adverse health effects, to establish a threshold level below which no adverse health effects are anticipated or, if a threshold cannot be established, to determine "the range of risk to humans resulting from current or anticipated exposure to the substance". Health & Safety Code §§39660 (b-c). OEHHA has failed to fulfill its obligation to calculate the potential health risks from outdoor exposure to ETS. OEHHA has not attempted to determine a threshold level of ETS in outdoor air below which no adverse health effects are anticipated; nor has it calculated the range of risks to human health from exposure to ETS in the ambient air in California.

The only risk estimates included in the OEHHA ETS analysis are the attributable risks for various health effects purportedly associated with ETS contained in Table 1.2. These risk

estimates are based on epidemiological studies of all ETS exposures, comprised largely of indoor exposure. OEHHA has made no effort to estimate the risks, if any, attributable exclusively to outdoor ETS exposures, as required by the Tanner Act and as calculated in all previous TAC listings.

The only estimate of the California public's exposure to ETS provided by the ARB is a roughly estimated exposure level that includes the sum of all exposures experienced in a 24 hour day, including both indoor and outdoor environments. ES-7. This exposure estimate is meaningless for the purposes of evaluating ETS as a TAC, as only outdoor exposure is relevant to a TAC listing determination. In other instances in which the ARB has considered both indoor and outdoor concentrations, it has segregated the impact of the two different exposures, and calculated health risks for indoor and outdoor exposures separately. For example, for formaldehyde, the ARB's listing recommendation stated the following at page 6, "[u]sing OEHHA's best value for unit risk of 7×10^{-6} ppbv $^{-1}$ and the corresponding dose rate for indoor and outdoor environments, the number of excess cases due to indoor and outdoor exposure to formaldehyde is estimated to be 230 and 5 per million, respectively. This corresponds to a cancer burden of 7,000 and 150 for indoor and outdoor exposures, respectively, for a California population of 30 million."

The Draft states that the only exposure for individuals that do not spend time with smokers is in outdoor locations, but does not attempt to estimate how often or at what levels such exposure might occur for Californians. As an accurate exposure estimate is a key component of an assessment of potential health risks, the absence of reliable exposure data makes it impossible

to establish a health risk attributable to ETS exposure in the ambient air. This stands in marked contrast to earlier ARB listing recommendations which included estimated potential risks attributable to outdoor airborne exposure to the candidate substance.

Respectfully submitted,

Brian J. McGinn

Commentary on Chapter 6 (Respiratory Health Effects) in Environmental Tobacco Smoke: Draft Staff Report of the California Environmental Protection Agency (Cal/EPA) (December 2003)

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PREFACE

Comment on 6.2.1.2. Asthma induction in adults

The Cal/EPA 2003 draft report's conclusion that ETS exposure is causally associated with "adult-onset" asthma is at odds with the judgements of a number of authoritative scientific bodies that have recently reviewed available epidemiological data on this topic. Cal/EPA should seriously and objectively reconsider its conclusion in regard to "adult-onset" asthma causation to conform to contemporary standards for such scientific judgements.

Cal/EPA's judgement is at odds with that of authoritative scientific bodies

The National Academies of Science' Institute of Medicine has very recently performed a thorough and exhaustive assessment of available evidence in regard to environmental factors that may cause or exacerbate asthma in adults and children (IOM – Clearing the Air 2000). The IOM report concluded that, among the many exposures considered, only house dust mite antigen had been demonstrated with sufficient evidence to cause the development of asthma. The IOM's consensus opinion in regard to ETS as a causative factor in the development of asthma in school-aged children, older children and adults was that there is *"...inadequate or insufficient evidence to determine whether or not an association exists..."* Similarly, IARC researchers had stated earlier (Tredaniel *et al.*, 1994) that it "*..remains controversial...*" whether indoor air ETS is associated with chronic respiratory symptoms and asthma. Neither did the 1986 report of the US Surgeon General, the 1986 NRC report, nor the 1992 EPA report on ETS conclude that the evidence for ETS was sufficient to support a causal inference for "adult-onset" asthma.

The remarkable Cal/EPA draft assertion that "adult-onset" asthma has been shown conclusively to be causally-associated with ETS exposures falls far short of the standards for such scientific judgements and should be withdrawn in a draft revision.

The etiology of asthma is only *incompletely understood*, and is *far too complex* to justify a simplistic inference of causation from a limited number of inconsistent epidemiological studies having inadequate confounder adjustments and at best weakly positive statistical associations with indoor air ETS exposures.

A bewildering genetic heterogeneity underlies the development of asthma; the scientific literature contains hundreds of genetic association studies on asthma-related phenotypes, with variants in 64 genes reported to be associated with asthma or related traits in at least one study (Hoffjan, Nicolae, and Ober 2003). None of the nine new studies cited in the Cal/EPA 2003 draft included consideration of this variable in the diverse study populations.

While the new epidemiological reports cited by Cal/EPA in support of a causal inference for "adult-onset" asthma in association with ETS exposure included some adjustments for confounders, none of the individual studies has come close to adequately considering the full spectrum of diverse associations that have emerged as potentially potent confounders for this complex disease. One example of such an emerging confounder is described in a very recent systematic review of extant literature that found that aspirin-induced asthma is detectable in fully 21% (14-29%, 95% C.I.) of adults when definitive oral provocation testing is conducted (Jenkins, Costello, and Hodge 2004). Notably, only about 3% (2-4%, 95% C.I.) of adults in this analysis were aware of such aspirin sensitivity and reported it at interview. This recent observation documents the

imprecision and limited utility of self-reported symptoms in diseases of extraordinarily complex etiology such as asthma, and indicates that simplistic inferences of causation based upon such data are unlikely to be correct. Among the new "adult-onset" asthma reports cited by Cal/EPA (2003), 7 of 9 studies employed unreliable self-reported asthmatic symptoms or self-reports of asthma diagnosis. Notably, the two cited studies that included more objective physician-diagnosed asthma data (Kronqvist, 1999; Flodin, 1995) did not report statistically significant associations of asthma and ETS exposure. Cal/EPA should objectively consider the available data on the unreliability of such self-reported asthma symptoms in drawing conclusions of causation that are at odds with those made in previous and more rigorous assessments by other scientific and public health bodies.

Clinical studies of asthmatics exposed to experimental ETS have strongly suggested that reactions to ETS do not occur by the IgE-mediated mechanism that is a hallmark of classic allergic asthma (Lehrer, Rando, and Lopez 1999). A minor subset of study subjects reporting ETS sensitivity and having clinically-diagnosed asthma have been shown to react to experimental levels of ETS exposure with modest reductions in FEV_1. However, the detected responses appeared to be attributable largely to sensory irritation by constituents of the ETS gaseous phase and exhibited a clear exposure-response relationship for measurable effects in ranges far higher than those typically encountered (Lehrer, Rando, and Lopez 1999).

In the following text, the conclusions of Cal/EPA are addressed as summarized below:

1. Asthma is an exceedingly complex and incompletely understood disease; simplistic conclusions regarding its etiology, based upon weak statistical associations with environmental exposures, are at best tenuous.
2. The contention that ETS induces asthma in adults is supported by neither the weight and strength of available epidemiological evidence, nor by a compelling body of mechanistic evidence. No authoritative consensus judgement regarding causation of adult onset asthma by ETS has been made previously by any expert scientific/public health organization.
3. The entire body of available epidemiological data, including the nine new studies cited in the Cal/EPA 2003 document, is an entirely insufficient basis for a reasonable scientific conclusion of a causal association between ETS exposure and induction of adult asthma.
4. Major asthma risk factors include family history of atopic disease, atopy, exposure to house dust mites, cat dander, cockroach antigens and childhood obesity. The potentially confounding effects of these major asthma risk factors are difficult to control for in any epidemiological study.
5. ETS and respiratory health studies are difficult to conduct and interpret.
6. Real-world levels of ETS exposure, and particularly outdoor air levels, are trivially low.
7. The draft conclusion that ETS exposure causes "adult-onset" asthma is not consistent with contemporary scientific standards and should be withdrawn.

MAJOR ASTHMA RISK FACTORS

Boushey *et al.* (2000) provide the following descriptions of asthma risk factors:

"The strongest is a family history of atopic disease."

"Atopy greatly increases the risk of asthma."

"This has best been established for the house dust mite...Other allergen exposures linked to a heightened risk of asthma are cat dander, cockroach, ..."

"In Britain and the United States, the rise in asthma among children has been accompanied by an almost epidemic increase in the prevalence of obesity."

A very recent longitudinal study of "adult-onset" asthma among members of a New England HMO found that new-onset asthma cases were overwhelmingly more likely to have occurred in association with infection than in association with workplace/environmental exposures (Sama *et al.*, 2003).

Therefore, it is very important in any ETS-asthma epidemiological study to account and adjust, fully and accurately, for the major risk factors for asthma. The available studies to date that are cited by Cal/EPA do not fully meet this requirement.

DIFFICULTIES IN CONDUCTING AND INTERPRETING ETS AND RESPIRATORY HEALTH STUDIES

ETS and Respiratory Health in Adults

Respiratory diseases and symptoms in either healthy or compromised adults exposed to ETS have not been as widely studied as they have been in children. No clear picture emerges from an analysis of the published papers on this subject, because the literature reports positive and negative associations as well as non-associations.

The ETS studies on adult respiratory health are influenced by many of the same potential confounders as the childhood studies, but there are at least 5 factors that may be of increased importance in considering design of ETS studies in adult populations: 1) Presence of adult lifestyle confounders (*e.g.*, alcohol consumption, dietary habits, hobbies such as woodworking and ceramics, *etc.*). 2) Occupational exposures to lung irritants. 3) Difficulty in obtaining accurate lifetime medical histories. 4) Greater difficulty in estimating current and past ETS exposure because of the increased mobility of adults. 5) Increased possibility of psychological aversion to ETS, resulting in exacerbation of reported symptoms (Smith *et al.*, 1992).

In addition to the potential confounders noted above, a number of possible biases are important considerations in ETS studies. These biases include misclassification of smokers as nonsmokers, reporting bias including recall bias, and diagnostic bias.

ANALYSIS OF NINE ASTHMA STUDIES NOT CONSIDERED IN 1997 Cal/ EPA DOCUMENT

The Cal/EPA 2003 draft report states that the 1997 OEHHA report reviewed studies evaluating the relationship between ETS exposure and chronic pulmonary disease among adults, including asthma. They concluded "... ETS exposure may make a significant contribution to chronic respiratory symptoms in adults." Although the OEHHA reported in 1997 on five studies purportedly supporting an association between ETS exposure and "adult-onset" asthma (Dayal *et al.*, 1994; Greer *et al.*, 1993; Leuenberger *et al.*, 1994; Ng *et al.*, 1993; Robbins *et al.*, 1993) no specific conclusions were articulated about asthma *per se*. Cal/EPA 2003 presents nine recent epidemiological

studies that evaluated the impact of ETS exposure on new-onset adult asthma and, remarkably, draws an affirmative causation conclusion.

The nine studies listed in Cal/EPA 2003 Table 6.14 have been reviewed and a summary of their design features is listed in Tables 1 and 2 with written comments following. Table 1 lists author/reference, study type, variables tested, population studied, and country. In addition, Table 1 summarizes criteria used to establish smoking status (smoker vs non-smoker), lab confirmation of smoking status, ETS exposure assessment, and known (established) home and occupational exposures/confounders. Where possible, Table 2 summarizes author definition of asthma and assessment/diagnosis of asthma. Categorizations include self-reported asthma or symptoms of asthma; self-reported physician diagnosed asthma; physician diagnosed asthma; and medical (clinical testing) confirmation of asthma.

An analysis of Tables 1 and 2 (attached) shows the inadequacies of the nine additional epidemiological studies regarding the purported contribution toward a conclusion of a causal association between ETS and adult onset asthma. For example, all nine studies rely on questionnaires, with only one study fully incorporating examination-based physician diagnosed asthma, and none fully confirm smoking status by laboratory test. In addition, only three of the nine studies are prospective in design, with the remainder being either cross-sectional or case control. Therefore, the study designs generally do not facilitate control for recall bias and preclude determinations of causality. Cross-sectional studies are, in any event, inappropriate for the development of inferences of causation and temporal relationships between purported exposures and effects.

Kronqvist et al., 1999

A large population-based cross-sectional study examined risk factors associated with asthma and rhinoconjunctivitis in 461 Swedish farmers. The farmers received a medical examination comprising a skin prick test (SPT), radioallergosorbent test (RAST) analyses, and lung function measurements. A questionnaire established symptoms and exposures. Subjects with a history of episodic shortness of breath, wheezing, and breathing difficulties were defined as having asthma. Allergen sensitization, especially to mites (OR=5.8 vs OR=3.8) and pollens (OR=10.3 vs OR=5.8) was significantly associated with asthma and rhinoconjunctivitis, respectively, in this farm community. Exposure to ETS in childhood and current exposure did not seem to affect the risk of allergen sensitization among either smokers or nonsmokers. No ETS data were given.

Cal/EPA 2003 Comments

"By postal questionnaire, asthma was defined as self-reported episodic respiratory symptoms, such as wheezing and dyspnea. ETS exposure was assessed for the current period (home and work) and during childhood. In this study, no measure of ETS exposure, past or present, was associated with the risk of asthma (OR or RR were not reported) (Table 6.14)."

Heck *et al.* Comments

The study was relatively large and included 461 Swedish farmers receiving medical exam, SPT, RAST analyses and lung-function measurements. The authors noted the following: "Reported exposure to environmental tobacco smoke in childhood or currently did not significantly affect the risk of airway disease in smokers, ex-smokers, or nonsmokers."

Iribarren et al., 2001

This large cross-sectional study examined *current* exposure to ETS and the association with personal characteristics and self-reported health conditions as determined from a multiphasic health check-up between 1979 and 1985. A total of 47,472 adult never-smoking members of the Northern California Kaiser Permanente Health Plan undergoing multiphasic health check-ups between 1979 and 1985 participated in the study. A written questionnaire was used to record duration and location of ETS exposure. Although it is not clear exactly when the ETS exposure data were collected it appears at least partially retrospective. The authors conclude ETS exposure correlates with several personal characteristics potentially associated with adverse health outcomes. They state ETS exposure was associated with several self-reported acute and chronic conditions but that the study design precluded causal inference.

Cal/EPA 2003 Comments

"Using a written questionnaire, current ETS exposure was ascertained for several locations: home, other small spaces (e.g., office or car), and large indoor spaces (e.g., restaurant). In each location, the survey assessed average duration of exposure. In both men and women, any ETS exposure was associated with a greater risk of self-reported physician-diagnosed asthma or hayfever (OR 1.22, 95% CI 1.11-1.34 and OR 1.14; 95% CI 1.06-1.24, respectively), controlling for socioeconomic and demographic covariates. The risk estimates were similar for high level exposure ($\geq$ 40 hours/week) compared to no exposure. For weekly exposure duration, there was evidence of an exposure-response relationship among women but not men."

Heck *et al.* Comments

The authors noted the following limitations:

"ETS exposure correlated with several personal characteristics potentially associated with adverse health outcomes."

"Firstly, the design was cross-sectional, precluding temporal associations and inferences about cause and effect."

"Thirdly, the assessment of medical conditions relied on self reports; no attempt was made to determine the sensitivity or specificity against a gold standard of care or serological markers."

"Estimation of lifetime exposure to ETS ...was not possible in this cohort because duration of ETS exposure was not ascertained."

"We found, unexpectedly, significantly lower odds of stroke among men reporting any ETS exposure at home or in large indoor areas."

"Another noteworthy finding was the lack of association of self reported cancer or tumour with any source of ETS exposure individually or with total ETS exposure in either gender."

The manner in which the Cal/EPA draft presents its abbreviated review of the paper of Iribarren *et al.*, (2001) is misleading in several respects, and should be revised to include and objectively discuss in their entirety the authors' peer-reviewed observations and conclusion that bear on whether ETS may be causally-associated with "adult-onset" asthma. These elements include the authors' admonition that cross-sectional studies such as that of Iribarren *et al.*, (2001) can not be legitimately employed to develop inferences of causation or temporal associations between environmental

factors and the occurrence of "adult-onset" asthma. The combination of "hayfever/asthma" for the purposes of this broad cross-sectional survey of health plan members unavoidably results in the combination of a variety of distinct disease conditions into a single symptom category. The selection of a few among the array of similarly weak and highly variable statistical associations among various lifestyle characteristics, behavioral traits, self-reported symptoms and ETS exposures reported in the original paper's Tables 4, 5 and 6 does not provide any reasonable basis for development of any conclusion of causation.

Larsson et al., 2001

A population-based study examined the impact of "at home childhood ETS exposure" on current self-reported physician-diagnosed asthma during adulthood. The participants included 8008 randomly selected adult never smokers (age 15-69) from Sweden. A questionnaire (postal survey) was used to estimate exposures, airway symptoms, and respiratory history. The authors concluded that, "childhood exposure to ETS is associated with an increased prevalence of asthma among adult never-smokers, especially in nonatopic subjects. Children exposed to ETS were also more likely to become smokers. ETS is a major lower airway irritant (LAWI)."

Cal/EPA 2003 Comments

"The prevalence of adult asthma was more common among subjects who indicated childhood ETS exposure (7.6%) compared to unexposed persons (5.8%) ($p=0.035$). Current self-reported "breathing difficulties from cigarette smoke" were also more common among subjects who indicated a history of childhood ETS exposure. In further analysis, the authors stratified by family history of asthma. Although there was no

clear impact of ETS among subjects without a family history of asthma, ETS exposure was associated with a greater risk of asthma among those with a positive family history (OR 1.82; 95% CI 1.28-2.58). These results could be consistent with higher rates of smoking cessation by asthmatic's parents, reducing exposure of their children with asthma."

Heck *et al.* Comments

Self-reported ETS exposure was assessed by the question, "Do or did any of your parents/relatives smoke at home when you grew up?" All questions were answered as either "yes," "no," or "not as far as I know." ETS exposures from smoking by parents or other relatives who actually live in the house is very different from that by relatives who occasionally drop by and smoke in the home. Also, there is no estimate of degree/intensity of exposure that may have occurred. It is unclear whether the self-reported current asthma began in childhood or is "adult-onset." Therefore, the relevance of these results to "adult-onset" asthma are also unclear.

The authors note "The difference in asthma prevalence between subjects exposed and not exposed to childhood ETS was more pronounced in the younger half of the population." The effect of recently-increased awareness of purported adverse effects of ETS on the accuracy or consistency of the reporting by younger subjects was apparently not considered as a potential source of bias in the study. "Wheezing" is not reported as significantly associated with ETS exposure. In fact, the p value for wheezing is 0.792, although wheezing is a hallmark symptom of asthma. Additionally, the authors state "We cannot exclude the possibility of reporting bias where asthmatics are more prone than nonasthmatics to report ETS exposure, which would give an overestimation of the risk"

and "...the association between active smoking and asthma is uncertain in the current literature."

Janson et al., 2001

This cross-sectional study aimed to evaluate the effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey. The study included 7882 adult (age 20-48) never smokers from 36 centers in 16 countries. The authors report "...passive smoking in the workplace was significantly associated with all types of respiratory symptoms and current asthma. No significant association was found between passive smoking and total serum IgE." The authors conclude that although, "passive smoking is common, the prevalence varies widely between different countries." The study reports, "passive smoking increased the likelihood of experiencing respiratory symptoms and was associated with increased bronchial responsiveness."

Cal/EPA 2003 Comments

"Compared with no ETS exposure, any ETS exposure at home or work was not associated with a greater risk of self-reported current asthma (OR 1.15; 95% CI 0.84; 1.58). When each source of exposure was examined individually, workplace exposure was related to a higher risk of asthma (OR 1.90; 95% CI 1.25; 2.88). There was no apparent impact of home exposure (OR 1.14; 95% CI 0.68; 1.90). These apparently discrepant results could be explained by the method of ETS exposure measurement. Home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. Because residence

with a smoker may not always reflect domestic ETS exposure (Eisner et al., 2001), use of this exposure measure could attenuate the effect estimate for home ETS exposure."

"The investigators also found a similar pattern of results for several asthma-like symptoms, including wheeze, nocturnal chest tightness, and dyspnea (nocturnal or exertional). In these instances, workplace ETS exposure was related to a greater risk of respiratory symptoms, whereas home exposure had no apparent impact. An exposure-response relationship was noted for all respiratory symptoms, but not clearly for asthma. Furthermore, both home and workplace ETS exposure were associated with greater bronchial hyper-responsiveness (assessed by methacholine challenge). Because bronchial hyper-responsiveness is a cardinal feature of asthma, this result adds additional support to the observed link between ETS exposure and self-reported asthma."

Heck *et al.* Comments

The study design was unblinded with "interview-led questionnaires." The percentage of cases classifiable as self-reported "adult-onset" asthma is unclear. Asthma was self-reported and subjects were not queried as to their age at onset and whether their reported asthma was physician-diagnosed. Thirty-six centers were studied, while only one used biomarkers of smoke exposure to validate nonsmoker status or ETS levels. The authors' abstract statement that "...passive smoking in the workplace as significantly associated with all types of respiratory symptoms and current asthma..." is inconsistent with the 95% confidence interval about the odds ratio and indicates a lack of statistical significance (odds ratio 1.90; 95% CI 0.90-2.88). No significant association was seen between asthma and overall ETS exposure, asthma and household ETS exposure and

ETS and total serum IgE. Reduction in lung function was not statistically significant in "ETS-exposed" participants. In addition, the authors note a number of study limitations including cross-sectional design, possibility of recall bias and reliance on self-reported exposure. Cross-sectional studies are not appropriate as a basis for the development of inferences of causation.

Flodin et al., 1995

A population-based case-control study from semi-rural Sweden evaluated smoking as a possible determinant of "adult-onset" asthma (age $\geq$ 20 yrs), controlling for other factors such as air pollution at work, dwelling conditions, and atopy. The authors compared 79 cases of asthma, diagnosed between ages 20 and 65, with 304 randomly drawn population controls of similar age from the same area as the cases. A questionnaire was used to collect information on smoking habits, occupational exposures, dwelling conditions, various suspect allergenic exposures, and atopy. The authors note, "those who had smoked for 3 years or more, present or past, were at increased risk for bronchial asthma (adjusted odds ratio = 1.9; 95% confidence interval = 1.1-3.3)." Exposure to ETS at work involved a slightly greater but statistically insignificant risk (OR 1.5; 95% CI 0.8-2.5).

Cal/EPA 2003 Comments

"A population-based case-control study from semi-rural Sweden evaluated ETS exposure as a risk factor for adult onset asthma (≥age 20 years). During a 9 month period, cases were identified from all persons filling a prescription for beta-agonist medications in two communities. The diagnosis of asthma was confirmed by a pulmonary specialist.

Controls were randomly selected from a general population register and matched to cases by age (of asthma diagnosis), gender, and community. ETS exposure at both home and work was assessed by written questionnaire, which was defined as exposure for at least 3 years prior to the age at asthma diagnosis (or comparable age for controls). Workplace ETS exposure was associated with an increased risk of asthma (OR 1.5; 95% CI 0.8-2.5), but the confidence interval did not exclude no relationship. Exposure to ETS at home was not associated with a greater risk of asthma (OR 0.9; 95% CI 0.5-1.5)."

Heck *et al.* Comments

This study examines 79 persons with asthma who were 20-65 years at diagnosis. The study does not appear to separately examine smokers and nonsmokers. The risk for adult asthma in association with three years of self-reported ETS exposure at work was nonsignificant (adjusted OR = 1.5, 95% CI = 0.8-2.5). At home the risk was actually less than 1.0 (OR = 0.9, 95% CI =0.5-1.9) for ETS-exposed subjects. Due to the reported lack of a statistically significant association and apparent failure to separately examine smokers and nonsmokers, this study does not support a causal association between ETS exposure and "adult-onset" asthma.

Thorn et al., 2001

A Swedish population based case-control study examined self-reported exposures to mold and ETS in the home environment and the risk of "adult-onset" asthma. The study was performed in a random population sample (n=15,813), aged 20-50 years. The adult onset asthma cases for the study included subjects self reporting "physician-diagnosed" asthma (n=174). Randomly selected referents (n=870) were chosen from the whole population sample. Exposures in the home environment, asthma, respiratory

symptoms, smoking habits, and atopy were obtained from a comprehensive mailed questionnaire. Authors reported "increased adjusted OR for asthma were associated with exposure to molds (OR 2.2, 95% CI 1.4-5.5) ETS (OR 2.4, 95% CI 1.4-4.1) and the presence of a wood stove (OR 1.7, 95% CI 1.2-2.5)."

Cal/EPA 2003 Comments

"A Swedish population based case-control study examined the impact of ETS exposure on "adult-onset" asthma (age $\geq$ 16 yrs). The investigators ascertained home exposure only, during or previous to the year of asthma diagnosis (and at a randomly selected time for control subjects). In this study, ETS exposure was associated with a greater risk of "adult-onset" asthma (OR 2.4; 95% CI 1.4-4.1). This increased risk was observed only among never smokers and not among current or ex-smokers. When the results were stratified by sex, the association was stronger for males (OR 4.8; 95% CI 2.0-11.6) than females (OR 1.5; 95% CI 0.8-3.1)."

Heck *et al.* Comments

The relative risks and confidence intervals for ETS (OR 2.4, 1.4-4.1) and mold (OR 2.2, 1.4-3.5) are so similar it raises the possibility that the two exposures are co-existent. The attribution of adult onset asthma to ETS may actually be confounded by mold which may or may not be evident to the subject. When the relative risks for males and females are reported separately, the relative risk for females for ETS and adult asthma is non-significant, 1.5 (0.8-3.1). The authors throw out data by starting with 251 cases of physician diagnosed asthma, then reducing the final subject number to 174 by arbitrarily reviewing only the period "between 1980 and 1994" purportedly to reduce recall bias. No report of the relative risks using the whole sample is given. When all

self-reported asthmatic symptoms are included in addition to self-reported physician diagnosed adult asthma, the risk becomes non-significant at 1.7 (1.0-2.8). The authors note the possibility of both under- and over-reporting of ETS exposure in their study design.

Hu et al., 1997

Asthma and related factors were evaluated in a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. Childhood ETS exposure to parental smoking was determined by parental reports. Seven years later during young adulthood, self-reported physician diagnosed asthma was determined using a written questionnaire. Family history was strongly associated with subjects' asthma (OR=3.1, 95% CI 2.4-4.5 for self reported physician-diagnosed asthma; OR=3.3, 95% CI 2.4-4.5 for current asthma). Exposure to parental smoking during childhood was significantly associated with self reported physician-diagnosed asthma (OR=2.9, 95% CI 1.6-5.6) and current asthma (OR=3.3, 95% CI 1.7-6.4). Also, self-reported mold growth at home was significantly associated with asthma (OR=2.0, 95% CI 1.2-3.2).

Cal/EPA 2003 Comments

"Evaluated a cohort of 1,469 seventh grade students seven years after a school-based smoking prevention program in southern California. At baseline, ETS exposure status was determined by parental reports of personal smoking. During young adulthood (seven years later), self-reported physician diagnosed asthma was ascertained by written questionnaire. Exposure to parental ETS at baseline was associated with an increased risk of subsequent asthma. Compared with no maternal smoking or light smoking at baseline

(< one-half pack per day), heavier maternal smoking was associated with an increased risk of self-reported asthma in young adulthood (OR 1.8; 95% CI 1.1-3.0). Similarly, heavy paternal smoking was related to a greater risk of asthma (OR 1.6; 95% CI 1.1-2.4). In addition, they observed an exposure-response relationship between number of parents smoking at baseline and the risk of asthma seven years later."

Heck *et al.* Comments

In this study, the age of onset for the reported asthma cases was not determined. Thus, the relevance of the findings to adult asthma onset is unclear. Also, in this study, like others, there is a potential selection bias in selecting the cohort for study in that "...These subjects originally participated in a school-based smoking prevention study in 1986." The possibility of the unblinded subject correlating the current asthma "yes" or "no" question with the previous smoking cessation program cannot be excluded.

Greer *et al.*, 1993; McDonnell *et al.*, 1999

A longitudinal cohort study of 3,914 adult non-smoking Seventh-Day Adventists living in California evaluated, by questionnaire, ETS exposure and the incidence of self-reported physician diagnosed asthma during a 15 year period. The authors reported the 10-year result (Greer *et al.*, 1993) as relating asthma to occupational and ambient air pollution in nonsmokers. Similarly, the 15-year cohort follow-up (McDonnell *et al.*, 1999) examined the incidence of asthma in nonsmokers with the long term ambient ozone concentrations. The Greer *et al.* (1993) study found: 1) ETS exposure significantly associated with the development of asthma (RR = 1.45; CI = 1.21 to 1.75), 2) airways obstructive disease before age 16 related to a marked increase risk (RR = 4.24, CI 4.03 to 4.45), and 3) an increased risk of asthma significantly associated with increased ambient concentration of ozone exposure in men (R = 3.12, CI = 1.61 to 5.85), but not in women. The study by McDonnell *et al.* (1999) suggested that long-term exposure to ambient ozone is associated with development of asthma in adult males. The only ETS exposure associated with asthma was in nonsmoking females only, with weak relative risk, 1.21 (CI=1.04-1.39).

Cal/EPA 2003 Comments

"As reported in the 1997 Cal/EPA report, duration of working with a smoker was associated with an increased risk of developing asthma (OR 1.5 per 10-year increment; 95% CI= 1.2-1.8). Since the 1997 Cal/EPA report, longer-term follow-up of the cohort has been reported. At 15-year follow-up, duration of working with a smoker was associated with an increased risk of incident asthma for women only (OR 1.21; 95% CI=

1.04-1.39). In both analyses, there was no reported relationship between duration of residence with a smoker and risk of asthma."

Heck *et al.* Comments

Greer et al., 1993

The representativeness of the Seventh Day Adventist (SDA) cohort to the broader California population is questionable. Furthermore, the prohibition of smoking by SDA church doctrine may increase the likelihood of smoker misclassification bias in this unique cohort. The ETS exposure is self-reported. The reported relative risk for adult asthma and ETS is very weak, RR 1.45 (CI =1.21-1.80). The subject numbers of incident asthma cases are small, that is, N =51 for females and N = 27 for males.

Only 13% of the potential respondents did not answer the questionnaire, but the final cohort is 2/3 female. Whether more females were initially queried is unknown. The average age at time of enrollment is relatively high, that is, 56.5. The plausibility that after a lifetime of ETS exposure without developing asthma, asthma is then induced after the age of 56.5 is questionable.

McDonnell et al., 1999

ETS was associated with asthma in nonsmoking females only, with a weak relative risk, 1.21 (1.04-1.39). In addition, the authors note that, "Misclassification of asthma status may have been greater in females than males," and that, "The degree of obstruction represented by FEV_1/FVC was considerably larger in males than females (Table 2), and only 27% of the new female cases reported use of asthma medication compared to 61% of the males." Therefore, the reported statistically significant ETS/female association is not consistent with the study's clinical observations.

Cal/EPA 2003 Comment (paragraph summarizing asthma induction discussion)

"There is no "gold standard" for defining asthma in epidemiological research. Although self-reported asthma is commonly used in survey research, this definition may not detect all persons with asthma (McWhorter et al., 1989; Toren et al., 1993). Respondents' reports of respiratory symptoms, especially wheezing, may have a greater sensitivity for identifying adults with asthma (Toren et al., 1993). Wheezing, in particular, correlates with the criterion of bronchial hyper-responsiveness (Burney et al., 1989)."

Heck *et al.* Comments

As shown in Table 1, there is significant heterogeneity in application of diagnostic criteria across the nine studies and in the general ETS asthma literature. While no diagnostic "gold standard" may be available, certainly minimum diagnostic standards should be used, as there is the possibility of a self-reported misdiagnosis especially with "adult-onset" asthma. Other conditions, for example the side effects of various drugs, could lead to a misdiagnosis. In general, actual physician diagnosis is superior to self-report. Cal/EPA is correct in stating that there is no universally-accepted and entirely objective definition of asthma in epidemiology. Yet while Cal/EPA emphasizes the possibility that self-reported "asthma-like" symptoms may under-represent true asthma incidence, a more scientifically objective view would acknowledge that an imprecise definition of diseases would just as likely lead to over-reporting of common viral or bacterial respiratory infections as "asthma". Cal/EPA should revise its draft wording to fairly and objectively consider this reality.

CONCLUSIONS

In summary, the nine new studies cited in the Cal/EPA 2003 document comprise: five foreign studies performed in populations and environments differing substantially from those of California; two studies of a Seventh Day Adventist cohort having numerous lifestyle differences from those of typical Californians; four cross-sectional studies inappropriate for the development of inferences of causality; eight studies lacking a complete medical confirmation of asthma diagnosis; and a variety of additional deficiencies discussed above and itemized in accompanying Tables 1 and 2. A number of the studies represented by Cal/EPA as demonstrating an association between ETS and asthma development did not in fact report consistent statistically significant associations.

The Cal/EPA draft conclusion that ETS exposure is causally-related to the induction of "adult-onset" asthma cannot be justified by scientific standards. No other authoritative scientific bodies around the world have rendered a similar judgement upon examination of available epidemiological data. The simplistic conclusion that exposure to ETS is causally related to a complex, multifactoral, and incompletely understood disease condition such as "adult-onset" asthma is not supported by a compelling body of extant epidemiological data or supportive temporal and mechanistic data and should be withdrawn by Cal/EPA in its revision of the draft 2003 report.

REFERENCES

Boushey, H.A., Corry, D.B., Fahy, J.V., 2000. Asthma, Chapter 39 in *Textbook of Respiratory Medicine*, Volume 2, Third Edition, J.A. Murray, J.A. Nadel (eds.), W.B. Saunders, Philadelphia, pp. 1247-1289.

California Environmental Protection Agency. 2003. Public Review Draft). Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, Part B: Health Effects. Chapter 6. Respiratory Health Effects, pp 1-104.

Dayal, H.H., Khuder, S., Sharrar, R., Trieff, N., 1994. Passive smoking in obstructive respiratory disease in an industrialized urban population. *Environ Res* 65(2):161-71.

Flodin, U., Jonsson, P., Ziegler, J., Axelson, O., 1995. An epidemiologic study of bronchial asthma and smoking. *Epidemiology* 6(5):503-5.

Greer, J.R., Abbey, D.E., Burchette, R.J., 1993. Asthma related to occupational and ambient air pollutants in nonsmokers. *J Occup Med* 35(9):909-15.

Hoffjan, S., Nicolae, D., Ober, C., 2003. Association studies for asthma and atopic diseases: a comprehensive review of the literature. *Respiratory Research* 4(1):14.

Hu, F.B., Persky, V., Flay, B.R., Zelli, A., Cooksey, J., Richardson, J., 1997. An epidemiological study of asthma prevalence and related factors among young adults. *J Asthma* 34(1):67-76.

IOM (Institute of Medicine), 2000. Clearing the Air: Asthma and Indoor Air Exposures. National Academy Press, Washington, DC.

Iribarren, C., Friedman, G.D., Klatsky, A.L., Eisner, M.D., 2001. Exposure to environmental tobacco smoke: association with personal characteristics and self-reported health conditions. *J Epidemiol Community Health* 55(10):721-8.

Janson, C., Chinn, S., Jarvis, D., Zock, J.P., Toren, K., Burney, P., 2001. Effect of passive smoking on respiratory symptoms, bronchial responsivemess, lung

function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. *Lancet* 358(9299):2103-9.

Jenkins, C., Costello, J., and Hodge,L., 1999. Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. *British Medical Journal* 328 (21 February):434-437.

Kronqvist, M., Johannsson, E., Perhage, G., Johannsson, S.G., van Hage-Hamsten, M., 1999. Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. *Allergy* 54(11):1142-9.

Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B, 2001. Enviromental tobacco moke exposure during childhood is associated with increased prevalence of asthma in adults. *Chest* 120(3):711-7.

Lehrer, S.B., Rando, R.J., and Lopez, M., 1999. The effects of environmental tobacco smoke on asthma: studies with a dynamic exposure chamber. In *Asthma: Causes and Mechanisms of an Epidemic Inflammatory Disease*, edited by T. Platts-Mills, Boca Raton, Florida: Lewis Publishers.

Leuenberger, P., Schwartz, J., Ackermann-Liebrich, U., Blasér, K., Bolobnini, G., Bongard, J.P., *et al.* 1994. Passive smoking exposure in adults and chronic respiratory symptoms (SALALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am J Respir Crit Care Med* 150(5 Pt 1):1222-8.

McDonnell, W.F., Abbey, D.E., Nihino, N., Lebowitz, M.D., 1999. Long-term ambient ozone concentraitonn and the incidence of asthma in nonsmoking adults: the AHSMOG study. *Environ Res* 80(2 Pt 1):110-21.

Ng T.P., Hui K.P., Tan W.C., 1993. Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. *J Epidemiol Community Health* 47(6):454-8.

Robbins A.S., Abbey D.E., Lebowitz M.D., 1993. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int J Epidemiol* 22(5):809-17.

Sama, Susan R., et al., Environ Health: A Global Access Science Source 2 :10 (2003).

Smith, C. J., Sears, S. B., Walker, J.C., and DeLuca P.O. 1992. Environmental tobacco smoke: Current assessment and future directions. *Toxicologic Pathology*. 20(2): 289-305.

Thorn J, Brisman J, Toren K (2001). "Adult-onset" asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy* 56(4:287-92.

Tredaniel, J., Boffetta, P., Saracci, R., Hirsch, A., 1994. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur Resp J* 7:173-.

Table 1. Summary of Exposure and Risk Factors: Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	*Country*	Study Type And Year conducted	Variables Tested	*Population*	Smoking Status Smoker vs Nonsmoker	Smoking status confirmed by lab test	Exposure to ETS	Known Home exposures/ con-founders considered	Known Occupational exposures/ con-founders considered
Kronqvist et al., 1999	Sweden	Cross-sectional 1996	Risk Factors	Population based 15-65 years dairy farmers (n=461)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire (especially for farmers)
Iribarren et al., 2001	Northern California USA	Cross-sectional 1979-1985	ETS esposure / personal characteristics	Lg health plan participants Never smokers 16,524 men (15-89) 26,197 women (15-105)	Questionnaire	No Subset only	Questionnaire (year collected not clear)	Questionnaire "lifestyle" factors	Questionnaire
Larsson et al., 2001	Orebro, Sweden	Population 1995-1996	ETS childhood exposure	Total of 8008 random inhabitants (15-69)	Questionnaire	No	Questionnaire	Some	Questionnaire
Janson et al., 2001	Europe	Cross-sectional 1990-1994	Passive smoking	7882 adults from 36 centres in 16 countries 3486 men; 4396 women (age 20-48) "never-smokers"	Questionnaire Self report	No	Questionnaire	Interview/ questionnaire "lifestyle" factors	Questionnaire Semi quant estimate from matrix of 350 occup. groups. Noted as none, low or high.
Flodin et al., 1995	Sweden	Case control 1990	Smoking	Population based 79 (20-65 yrs) w/ asthma 304 controls (age/sex)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Thorn et al., 2001	Alvsborg, Sweden	Retrospective case control 1994	Mold or ETS	Population 15,813 (age 20-50)	Questionnaire	No	Questionnaire	Questionnaire	Questionnaire
Hu et al., 1997	LA and San Diego California USA	Cohort 1993	Asthma related factors	n=2041 age 20-22	Questionnaire Self report	No	Questionnaire	yes	Not noted
Greer et al., 1993	SF, LA or San Dieo California USA	Long term prospective Cohort 1977; 1987	Occupational & ambient air pollution	n=3914 Adult (≥25 yrs) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Not noted	1987 included as part of questionnaire
Mc Donnell et al., 1999	SF, LA or San Dieo California USA	Longitudinal prospective cohort 1977; 1987; 1992	Long term ambient ozone concentration	n=3091 Adult (age 27-87) Non-smoking Seventh-Day Adventists	Questionnaire Self report	No	Questionnaire	Questionnaire	Questionnaire

Table 2. Criteria for Asthma Diagnosis : Nine Epidemiological Studies on "Adult-Onset" Asthma used in Cal/EPA 2003

Reference	Author Defined Asthma Symptoms	Questionnaire	Self reported Asthma or symptoms of asthma	Self Reported Physician Diagnosed	Physician Diagnosed Asthma	Medical Confirmation of Asthma symptoms
Kronqvist et al., 1999	History of episodic shortness of breath, wheezing, & breathing difficulties	yes	yes	no	yes	Allergic Disease Physician SPT (13 allergens) RAST (blood) Lung function test
Iribarren et al., 2001	Hay fever/ Asthma	yes	yes Hay fever/ Asthma	yes	no	Not noted
Larsson et al., 2001	Not noted	Yes – Developed from the British Medical Research Council questionnaire	Questions on many respiratory symptoms	yes	no	no
Janson et al., 2001	Not noted	1. Screening questionnaire 2. Interview led questionnaire	Questions on many respiratory symptoms	no	no	Blood tests total and specific IgE, spirometry, methacholine challenge
Flodin et al., 1995	American Thoracic Society	American Thoracic Society	Beta-agonist users	no	Selected cases confirmed with doctor	Examined by lung specialist
Thorn et al., 2001	Not noted	1. Screening questionnaire 2. Mailed comprehensive questionnaire	Questions on many respiratory symptoms	yes	no	no
Hu et al., 1997	Not noted	questionnaire	yes	yes	no	no
Greer et al., 1993	Not noted	Questionnaire developed by British Medical Research Council	Questions on many respiratory symptoms	yes	no	1987 "cases" – 1990 medical record/physician confirmation
Mc Donnell et al., 1999	American Thoracic Society	American Thoracic Society	Questions on many respiratory symptoms	yes	no	Lung function testing Spirometry Peak expiratory flow (PEF)

Dear Ms. Brooks,
I received a letter from the Air Resources Board today (Jan. 7 2004)and contacted Mr. Robert Kreiger (916) 327 5615. He suggested I write a letter outlining my experience with Second Hand Smoke (ETS), and my opinion, and send the results to you. I am not a health professional, but in fact a retired Mechanical Engineer who specialiced in a career dedicated to command and control hardware and software development on such programs as the Saturn Five Second stage checkout, and most recently, before retirement, I was the Aerospace Corporation responsible engineer for verification of the Global Positioning System (GPS) hardware and software as required by contract to the U.S. Air Force, from 1976 through 1993 when I retired after success rewarded by our team's winning the Collier Trophy in 1993. When my wife had a stroke, in 1993, I retired at age 68.

My experience with ETS starts with free cigarettes in the U.S. Navy in 1945 and the unusual result that I became a lifelong non-smoker. I was neither addicted to or an admirer of smoking. I couldn't stand the things. I gave my smoking friends all my cigarettes. My first wife was a smoker and we were married for 47 years. She smoked regularly (2 packs a day) and died of Colon Cancer in Jan. 2002, with all doctors agreeing that smoking had nothing to do with her Colon Cancer. I was exposed to ETS through both courtship and marriage for 56 years. I recently re-married to another smoker, so I have been exposed to ETS for 57 years. When is it going to cause some disease that will kill me? I'm now 79 and ETS has had no effect on me. If it shortens my life, I will still have lived longer than the average predicted by the Surgeon General (SG).

My background to comment on ETS is based on my reading as many SG reports as I could find, the text "Foundations of Epidemiology", the Program Description Document of SAMMEC, the program that is used to determine the "risk" of smoking, and a text by Steven J. Milloy (Science Without Sense" which de-bunks the EPA effort to use "Risk" as means of damning smoking. I have studied the difference in "proof " of cause as determined by Engineeering's Scientific Method, and "Risk" as indicating cause by medically favored Epidemiology. It is like Apples and Oranges, where "risk" is a mathematical simulation, and "cause" is the result of physical testing, not simulation. Steven Milloy's book has a Table that shows the "Risk" of ETS as 1.13, a value lower than the "Risk" of sudden heart attack from 3 cups of coffee a week!

While the Tome "Foundations of Epidemiology" states that Biological Credibility must support the Epidemiological findings (I cannot find ANY biological credibility to ETS as a report that proves ETS kills anything) it still leaves the door open if the "Risk" exceeds 3.0. But there is no Biological credibility to the claim ETS is a threat unless you consider the off-hand comment so often used that "ETS has 4,000 chemicals in it" some of which are known poisons. But the amount required of any of these chemicals to be dangerous is not mentioned, (the threat of poison is in the dose) and the amount produced is also not shown. The current value of (Risk) of 1.13 was reached by the EPA who was chastized in court for the method they used to even get that miniscule value by a judge Osteen. Careful review of the 34 "studies" making up the basis for the risk of ETS reveals two of the "studies" "Risk" value show ETS is GOOD for you! (less than 1.0). There is NO RISK to ETS. This was recognized until about 1980 when it became "unfashionable" to admit there is not only no scientific evidence, but also no risk from second hand smoke. An actual test report in 1972 shows that worst case, ETS totals 2 dozen cigarettes a year!.

The real problem with ETS is that no one worries about "cause" any more because Epidemioligical studies to determine "risk" are used instead of tests to find cause. That is why with all the hoopla about restricting smoking and de-toxing cigarettes, the American Cancer Society presents reports every year that estimate an increase in lung Cancer while smoking decreases. This indicates the Epidemiological findings are false.

The inflexible medical approach that rules out any possibility of escape from the "risk" of smoking is absurd in the face of people like me who are NOT addicted, do not react to ETS and also from smokers who smoke all their lives and die of old age, and people who NEVER smoke, avoid contact and die of lung cancer.

The above write up or report, stem from my own experience. I have noted others come to the same conclusions independently also. I feel that the loss of testing for cause has lost out to easy computer based studies that syphon off all the tax money that should be used to find "cause". Charles I. Klivans, now at 1203 West Bullock, Dennison TX 75020, 903 465 5828 , reno1933@cableone.net. After Feb. 22 this year I will be at my home in Redondo Beach CA 90277, 310 375 8038 , cklivans@jps.net I intend to sell my home in California, where nothing is good enough, to live with my new wife in Texas at the home above in Dennison, until something gets us!.

Charles I. Klivans

BILL LOCKYER
Attorney General

State of California
DEPARTMENT OF JUSTICE

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February 23, 2004

Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street
P.O. Box 2815
Sacramento, California 95812

Re: Draft Report: Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant

Dear Ms. Brooks:

Thank you for the opportunity to provide comments on the draft report, *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant*. The Tobacco Litigation and Enforcement Section of the Office of the California Attorney General is responsible for ensuring compliance with the Tobacco Master Settlement Agreement. The Attorney General's Office has focused on a number of issues concerning the health effects associated with exposure to environmental tobacco smoke. The report's summaries of the latest scientific research regarding environmental tobacco smoke, and Cal EPA's conclusions based upon these studies, will be extremely valuable to our continued enforcement efforts.

The agency is to be commended for compiling and analyzing all of the research contained in the report. The report provides a thorough and balanced review of the scientific literature on secondhand smoke, including the large number of studies that have been published since the release of Cal EPA's 1997 report on secondhand smoke.

As a law enforcement agency, the Attorney General's office appreciates the basic explanation of the medical terminology and illnesses discussed in the report. Providing definitions and background information on illnesses associated with ETS exposure is a significant aid in understanding the studies and clinical trials reviewed in the report.

The detailed descriptions of the particular studies, including their research methodology, findings, and possible confounding variables and other concerns, is very useful for examining individual studies that may be of special interest, and for reviewing the basis for the conclusions in the report. Further, collecting all of these studies in a single volume greatly simplifies the task of researching studies on ETS exposure.

We look forward to Cal EPA's continued examination of the health effects associated with exposure to environmental tobacco smoke.

Sincerely,

DENNIS ECKHART
Senior Assistant Attorney General
Tobacco Litigation & Enforcement Section

For BILL LOCKYER
Attorney General

PP:DE:cp

March 4, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
1001 I Street
Sacramento, CA 95812

Attention: Environmental Tobacco Smoke

Dear Ms. Brooks:

On behalf of the American Cancer Society, California Division, we are writing in strong support of the California Air Resources Board's proposal to identify environmental tobacco smoke (ETS) as a toxic air contaminant.

The scientific evidence demonstrating the health hazards of ETS has been overwhelming for years. ETS has been classified by the U.S. Environmental Protection Agency as a Group A carcinogen. Group A carcinogens include only the most dangerous substances such as asbestos and radon. ETS contains over 4,000 substances, more than 40 of which are known or suspected to cause cancer in humans and animals. Each year, about 3,000 nonsmoking adults die of lung cancer as a result of breathing ETS.

Enclosed for your reference is the American Cancer Society's Cancer Facts & Figures 2003. In addition, may we refer you to your colleagues in the California Department of Health Services, Prevention Section, Chronic Disease & Injury Control Branch, Tobacco Control Section. They possess a wealth of exposure and other ETS data more recent than the 1999 data cited in your report.

We believe that ETS, a proven air-borne carcinogen, should be classified as a toxic air contaminant. The evidence is unequivocal.

Should you have any questions or if we can be of any assistance, please feel free to contact us.

Sincerely,

Diane J. Fink, MD
Chief Mission Delivery Officer

State Government Relations Office
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2003

A DAY IN THE LIFE

Fighting Cancer 24/7

2003 Annual Report

to the People of

California on Progress

in Cancer Control

American Cancer Society

State of California

Memorandum

Department of Health Services

Date: March 8, 2004

To: Ms. Janette Brooks, Chief
Air Quality Measures Branch
California Air Resources Board
1001 I Street
P.O. Box 2815
Sacramento, CA 95812

From: Dileep G. Bal, M.D., Chief
Cancer Control Branch
Department of Health Services
1616 Capitol Avenue, Suite 74.516
P.O. Box 997413, MS 7202
Sacramento, CA 95899-7413

Subject: Environmental Tobacco Smoke (ETS)

This letter is in response to the draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003, Part A: Exposure Assessment" and its companion piece, "Part B: Health Effects." The California Department of Health Services, Tobacco Control Section (CDHS/TCS) believes that these reports by the California Air Resources Board (CalARB) and the Office of Environmental Health Hazard Assessment (OEHHA) are factual and use accurate data to reflect real world exposure and health effects from ETS.

We believe the report is scientifically accurate and believe that the evidence is convincing that ETS should be classified as a Toxic Air Contaminant (TAC). We hope that the Scientific Review Panel and the CalARB move forward in a timely manner classifying ETS as a TAC.

Although Californians have dramatically had their exposure to ETS decreased, ETS exposure is still too high. Some workers are still exposed on the job site, such as warehouse employees and waiters who work at facilities with patios. In addition, a number of employees are exposed in work vehicles. Even though the number of Californian smokers with rules banning smoking in their home has increased from 19.8 percent in 1993 to 49.0 percent in 2002, some children and spouses are still needlessly exposed in their home.

If you have any questions or comments, please contact David Cowling, Ph.D., Assistant Chief, Research Scientist, Data Analysis and Evaluation Unit, TCS, at (916) 449-5468.

Natural Resources Defense Council • The Breast Cancer Fund • San Francisco Bay Area Physicians for Social Responsibility • Breast Cancer Action • Los Angeles Physicians for Social Responsibility

March 29, 2003

VIA FACSIMILE: 916-327-7212

Janette Brooks, Chief
Air Quality Measures Branch
California Air Resources Board
1001 I Street / P.O. Box 2815
Sacramento, California 95812

Attention: Environmental Tobacco Smoke

Comments to the Office of Environmental Health Hazard Assessment (OEHHA) on the Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003.

The Natural Resources Defense Council, The Breast Cancer Fund, San Francisco Bay Area Physicians for Social Responsibility, Los Angeles Physicians for Social Responsibility and Breast Cancer Action appreciate the opportunity to comment on the OEHHA draft health effects assessment for environmental tobacco smoke (ETS). Our organizations are all actively involved in efforts to prevent significant environmental threats to public health.

The listing of ETS as a Toxic Air Contaminant (TAC) under Health and Safety Code sections 39650-39674 is a scientific "no brainer." There is a veritable mountain of scientific data showing that ETS is a significant health hazard, and is causally associated with cancer, cardiac disease, asthma, other respiratory disease, and developmental problems in children including Sudden Infant Death Syndrome (SIDS). It is absolutely clear that this chemical mixture qualifies for listing as a TAC. ETS contains numerous chemicals that are already listed as TACs, such as benzene, 1,3-butadiene, various polycyclic aromatic hydrocarbons (PAHs), acrylamide, ammonia, hexavalent chromium, formaldehyde, and lead. Another somewhat similar complex mixture, diesel exhaust, was listed as a TAC several years ago. Based on its list of ingredients, ETS could essentially be summarized as diesel exhaust with added nicotine and tobacco-specific nitrosamines (TSNAs). Therefore we strongly endorse the conclusions of the draft document and support the proposed listing of ETS as a TAC.

The draft health effects assessment is an agonizingly detailed review of the enormous scientific literature on ETS. Although the quality of the science is high, and we believe that the document accurately reflects the literature, we are deeply concerned that this review sets a standard that is ultimately detrimental to public health. Spending the decade of research and the thousands of

person-hours required to create a document that is this lengthy and detailed for a TAC listing determination inevitably means that very few chemicals or mixtures will move through the listing process. As California implements increasingly severe budget cuts, it is likely that OEHHA will suffer from worsening staff shortages. If every document is expected to be a multi-volume review comparable to this draft, we will see very little activity toward listings of environmental hazards.

A prior document listing ETS as a toxic air contaminant was fully endorsed by the Scientific Review Panel in June of 1997. This document was begun in June of 2001 and was in process for two and a half years, during which time the California Air Resources Board did not have the authority to regulate ETS as a toxic air contaminant. Meanwhile, as we can see from this draft, we can reliably state that while this document was being written about three thousand children were born in California with low birthweight due to ETS exposures, three hundred infant deaths from SIDS occurred, hundreds of thousands of people suffered otherwise potentially preventable asthma exacerbations, and thousands of deaths from myocardial ischemia occurred due to exposures to ETS. Some number of these illnesses might have been prevented had ARB been granted the regulatory authority sooner to take aggressive action against ETS. It is therefore necessary for OEHHA to balance scientific thoroughness with its mandate to implement the laws designed to protect public health.

We firmly believe that it is possible to produce a high quality scientific review that is a fraction of the length of this document, and that could be completed in a small fraction of the time. There is nothing in the law or the science that requires OEHHA to produce a definitive encyclopedia on the effects of every chemical that it reviews. It is only the fear (and reality) of industry litigation, and the creeping precedent of ever-larger reports that drive OEHHA to such extremes in document preparation. Shorter review documents would save the time and effort of the agency scientists, and of the reviewers charged with reading the documents. Shorter documents can be just as accurate scientifically and can be much more useful for protecting public health, since five such documents could potentially be produced in the time spent on one document such as the one reviewed today.

Due to the extreme length of the document, we focused our review on the introductory material and the discussion of ETS and breast cancer. Although there are likely other important and interesting issues throughout the rest of the draft, we were simply unable to give these chapters the review they deserved in the time available.

Petition to Bring ETS before the DART Identification Committee

Although we did not focus our current review on Chapters 3-5 of the document, we could not help noticing that there is now even more extensive evidence demonstrating that ETS is a reproductive and developmental toxicant. In the interest of 'reducing, reusing, and recycling' this document, and in the hope of further protecting the public from this extremely hazardous exposure, we therefore petition OEHHA to take ETS out of the normal glacial prioritization process and to present these three chapters to the Developmental and Reproductive Toxicant

Identification Committee at its next meeting for reconsideration of the listing of ETS under Proposition 65 [California
Health and Safety Code 25249.5 et *seq]*

Comments on Chapter 1

The definition of ETS is somewhat inconsistent with the discussion on page 1-4 and 1-5 about ETS exposure in animal studies. The latter discussion appears to state that only 'sidestream smoke' is relevant to ETS exposure, whereas the definition on page 1-2 makes clear that ETS is actually comprised of 'mainstream smoke' that escapes when the smoker inhales, exhaled mainstream smoke, and sidestream smoke. Thus the animal tests that carefully expose animals only to sidestream smoke do not appear to reflect the full range of realistic exposures to ETS. It is incorrect to say that "A few recent studies have used exposures characterized as 'sidestream smoke,' which is considered more relevant to the assessment of the effects of ETS exposure." In fact, a mixture of mainstream and sidestream smoke would be most relevant. Although this point is a minor one, it bears correcting to avoid the appearance of dismissing animal data that do not include only sidestream smoke. In reality, virtually all of the animal experiments could be classified as exposures to ETS at various doses.

The discussion of measures of effect and weight of evidence evaluations on pages 1-5 through 1-7 is very useful. It does make sense to evaluate the quality of the studies and the sources and likely direction of any bias when evaluating the weight of evidence. It is also important not to dismiss studies that failed to achieve statistical significance at the 0.05 level, since such studies may indeed be affected by factors such as insufficient power or by extensive nondifferential misclassification of exposure. We also agree that inconsistencies in scientific results are almost inevitable in any body of research, and that the finding of results that are not consistent from one study to another should not be a reason to automatically dismiss the results or to give up and declare that 'the jury is still out' on an issue. Instead, it makes sense to try to determine if there may be explanations for the inconsistencies and to see if it is still possible to draw conclusions based on the entirety of the available evidence. It is helpful for OEHHA to explain these important issues in the introductory material to avoid confusion about how the draft was prepared, and to help members of the public understand these important scientific issues. We believe that this discussion reflects a thoughtful approach to the literature review that is well-justified scientifically.

Comments on Chapter 7 Section on Breast Cancer

We applaud OEHHA for the groundbreaking review of the links between ETS and breast cancer on pages 7-91 to 7-155, and we agree with the conclusions reached. There has been a lot of important research over the past few years into this important issue, and the weight of evidence points strongly toward a causal association. The large majority of the epidemiologic studies found elevated odds ratios, although not all were statistically significant. The studies with the best efforts at exposure assessment found greater odds ratios and were more likely to achieve

statistical significance, in keeping with the prediction that nondifferential misclassification of exposure status tends to bias toward the null. The literature on active smoking and breast cancer supports the unifying hypothesis that tobacco smoke is an important breast cancer initiator, but is also anti-estrogenic and therefore has an anti-promotor effect. Therefore the timing of the exposure becomes extremely important. Among smokers, exposure when the breast is still particularly vulnerable to carcinogens before pregnancy and lactation, appears to be clearly associated with breast cancer development, whereas exposure after pregnancy and lactation and in the postmenopausal period has the opposite effect, especially in overweight women who would normally have higher levels of circulating endogenous estrogens after menopause.

It is clear that tobacco smoke contains numerous chemicals that cause mammary tumors in laboratory animals. In addition to the fifteen chemicals listed in Table 7.4D, the following seven chemicals should also be added: acrylamide, isoprene, N-nitrosodiethylamine [1], propylene oxide, cadmium [2], nitromethane [3], and nitrobenzene [4].

The findings of PAH-DNA adducts in humans exposed to environmental sources of polycyclic aromatic hydrocarbons, including cigarette smoke (ie. the Whyatt et al. study cited on page 7-136 and the Rundle et al. study described on page 7-91) are a helpful part of the causal chain. The fact that the PAH-DNA adducts do not appear to be a biomarker that is highly specific to cigarette smoke is not surprising, given the other environmental and dietary sources of this pollutant. Yet the finding of these adducts in human tissues, particularly in breast cancer tissues, does add to the overall weight of evidence, since we know that cigarette smoke is one important source of PAH exposure.

There are a couple of inconsistencies between Table 7.4E on page 7-141 and the text that follows. In particular, the table classifies the Hirayama 1984 study and the Jee 1999 study as 'unlikely' to have missed important exposures to ETS. Yet in the subsequent tables these same studies are classified as 'likely' to have missed important ETS exposures. Because both studies looked only at the husband's smoking history, it seems at first glance that they should be classified as likely to have missed important exposures. However, since both studies were done in Korea during a time when perhaps it may have been unusual for women to work outside the home, occupational exposures may have been unlikely and such a history unnecessary. Still, it seems that the complete neglect of ETS exposures during childhood would merit classification of both studies in the 'likely' to have missed important exposures category, unless cigarette smoking was very unusual in Korea in the 1930's-1950's. At any rate, these studies should be classified consistently as either likely or unlikely to have missed important ETS exposures.

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[1] 9th Report on Carcinogens. US Department of Health and Human Services, Public Health Service, National Toxicology Program, 2000.
[2] IRIS http://www.epa.gov/iris/search.htm. Note that cadmium causes mammary tumors in male rats only.
[3] ToxNet (CCRIS-Chemical Carcinogenesis Research Information System): http://www.nlm.nih.gov/pubs/factsheets/ccrisfs.html
[4] Gold LS, Neela B. Manley, Thomas H. Slone, Jerrold M. Ward. Compendium of Chemical Carcinogens by Target Organ: Results of Chronic Bioassays in Rats, Mice, Hamsters, Dogs, and Monkeys Toxicologic Pathology 29: 639-652 (2001).

In this draft document, OEHHA calculates estimates of ETS-related morbidity and mortality due to a list of diseases, including California-specific figures for childhood asthma induction and exacerbation, bronchitis or pneumonia in children, lung cancer, SIDS, low birth weight, and otitis media. Yet for some reason, OEHHA fails to calculate estimates of ETS-related morbidity and mortality due to breast cancer. Such an omission makes no sense. OEHHA concludes correctly that the data support a causal association between ETS exposure and breast cancer. OEHHA is also able to calculate a summary statistic of the overall magnitude of the risk (a relative risk of 1.92 when all important ETS sources are collected). The overall population burden of breast cancer in California is well known. Therefore it would be straightforward to calculate the attributable fraction of breast cancer due to ETS. We searched the draft in vain for such a calculation and finally concluded that the calculation was omitted. It is critically important for the public to know the proportion of breast cancer occurrence in California that would potentially be eliminated if exposure to ETS were prevented. Breast cancer is unfortunately all too common, and any public health intervention that may decrease the burden of this disease in California is of utmost importance. Therefore we strongly urge OEHHA to add a calculation of the attributable risk for breast cancer and ETS to the final version of this document.

Thank you for your consideration of these comments.

Sincerely,

Gina M. Solomon, M.D., M.P.H.
Senior Scientist, Natural Resources Defense Council

/S/
Barbara Brenner, Executive Director
Breast Cancer Action

/S/
Jeanne Rizzo, Executive Director
The Breast Cancer Fund

/S/
Bob Gould, M.D., President
San Francisco Bay Area Physicians for Social Responsibility

/S/
Jonathan Parfrey, Executive Director
Los Angeles Physicians for Social Responsibility

Natural Resources Defense Council (NRDC) uses law, science, and the support of more than 550,000 members nationwide (over 110,000 members in California) to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things.

Breast Cancer Action (BCA) is a national, grassroots organization with over 8,000 members in California, committed to true prevention of breast cancer through identification of and policy changes to address environmental links to the disease.

The Breast Cancer Fund (TBCF) identifies -- and advocates for elimination of -- the environmental and other preventable causes of the disease. Founded in 1992, TBCF works from the knowledge that breast cancer is not simply a personal tragedy, but a public health priority that demands action from all.

Physicians for Social Responsibility, Los Angeles (PSR-LA) is a local affiliate of the national organization, Physicians for Social Responsibility (PSR). We are dedicated to creating a world free of nuclear weapons, global environmental pollution, and gun violence.

Physicians for Social Responsibility, San Francisco Bay Area Chapter (PSR-SF) – is a nonprofit educational organization committed to the elimination of nuclear and other weapons of mass destruction, achievement of a sustainable environment, and reduction of violence and its causes.

5 March 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street / P.O. Box 2815
Sacramento, California 95812

Dear Ms. Brooks:

Following are my comments on the draft report, *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003*. In general this report, which contains CARB's initial evaluation of exposure and an assessment of the potential health effects resulting from this exposure is very well done, and contains much useful information and valid conclusions, particularly concerning breast cancer causation by Environmental Tobacco Smoke (ETS). As you know, there have been few measurements of ETS reported in outdoor microenvironments, and to the best of my knowledge, there are no published data on outdoor carcinogen levels from ETS. I have recently collected indoor/outdoor PPAH data while on a cruise ship in the Caribbean. A preliminary report on this data follows.

Sincerely,

James Repace, MSc.
Health Physicist

Indoor/Outdoor PAH Carcinogen Pollution on a Cruiseship in the Presence and Absence of Tobacco Smoking

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and
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abstract

A contribution to the exposure assessment of secondhand smoke (SHS) in outdoor microenvironments is made by measuring a class of carcinogenic compounds emitted during tobacco combustion, particulate polycyclic aromatic hydrocarbons (PPAH). Using a personal exposure monitor for PPAH, measurements were made on a gas-turbine-powered cruise ship underway in the South Atlantic to eliminate the omnipresent background of PPAH due to diesel emissions in urban environments. A controlled experiment was conducted using a human smoker in a well-ventilated inside stateroom to assess the PPAH emission from both exhaled mainstream and sidestream smoke from the most commonly smoked brand of cigarette, Marlboro. These cigarettes are estimated to emit ~15 micrograms of PPAH when smoked, or ~21 micrograms per gram of tobacco consumed. Peak levels of PPAH after 6.7 minutes of smoking had increased 100-fold. Two field surveys were conducted indoors and outdoors on the ship in the presence and absence of tobacco smoking. The number of cigarettes, pipes, and cigars within 30 ft of the monitor were recorded. Steady tobacco smoking in various smoking-permitted outdoor areas of the ship tripled the level of PPAH to which nonsmokers were exposed relative to indoor and outdoor areas in which smoking did not occur, despite the strong breezes and unlimited dispersion volume. Moreover, outdoor smoking areas were contaminated with PPAH to nearly the same extent as a popular casino on board in which smoking was permitted. SHS PPAH in outdoor environments are readily detectable, and measurably increase the exposure of outdoor hospitality workers, such as waitstaff, bartenders, and musicians, to a class of compounds heavily implicated in tobacco carcinogenesis.

Introduction: The State of California Air Resources Board (CARB) has proposed to identify environmental tobacco smoke (ETS), also known as secondhand tobacco smoke (SHS), as a toxic [outdoor] air contaminant. The first step is to determine if it is toxic and to estimate public exposure (CalEPA, 2003). As CARB has stated, studies measuring outdoor ETS contaminants are limited. This work increases the body of knowledge concerning ETS contamination of outdoor air by measuring particle-bound polycyclic aromatic hydrocarbons (PPAH) in indoor and outdoor air on a

gas-turbine powered cruise ship in the South Atlantic. This venue was chosen in order to eliminate the contribution of PPAH from vehicle exhaust common in cities.

The toxicity of polycyclic aromatic hydrocarbons (PAH) is well known; PAH are a class of carcinogens formed in the incomplete combustion of organic material, including tobacco smoke, broiled foods, and polluted industrial environments. Iron and steel foundry workers exposed to PAH have elevated rates of cancer. PAH are potent carcinogens in laboratory animals, inducing upper and lower respiratory tract cancers when inhaled, and digestive tract tumors when ingested (Hecht, 2004). Total PAH include both gaseous and particulate phase compounds. A subset of PAH, particle-bound PAH or PPAH, consists of a mixture of well-known carcinogens present in tobacco smoke, as well as diesel exhaust, and wood smoke (Hoffmann & Hoffmann, 1987). PPAH have been implicated in heart disease and stroke mechanisms as well (Glantz & Parmley, 1991). The classic PPAH compound is benzo(a)pyrene, which is a known human lung carcinogen (Danissenko, et al., 1996). There are >100 PAH molecules; measurement of PPAH underestimates the total number of toxic PAH in the air.

Portable real-time PAH monitors have been developed, calibrated against standard gas-chromatography /mass spectrometry methods, and deployed in environmental epidemiology studies (Zhiqiang et al., 2000; Chuang et al., 1999; McBride et al., 1999; Repace et al., 1998; Ott et al., 1994, McDow et al., 1990, Hart, et al., 1993). A lightweight battery-powered, real-time, data logging respirable PPAH monitor, the EcoChem PAS2000CE (EcoChem Analytics, Inc., League City, TX) is deployed in these experiments. The PAS2000CE monitor has a pump which passes a particle-laden aerosol at the rate of 1 liter per min into a double-walled quartz tube around which is placed an excimer lamp filled with krypton and trace amounts of bromine. When a voltage is applied, the lamp emits ultraviolet light at a wavelength of 207 nanometers, which causes an electronic process in surface-bound PAH which absorb the energy and are promoted into an excited state. This excited state results in "Auger emission" of a photoelectrons which ionize oxygen atoms in the air, leaving behind positively charged ions which are separated out and collected in the filter element of an electrometer, causing an electric current to be measured and logged. This photoelectric charging gives a signal which is proportional to the absorbing surface and its chemical composition. The monitor is

calibrated by the manufacturer (Ecochem Analytics; Siegmann and Ott, in preparation).

Ott and Repace (2003) calibrated the Ecochem PPAH monitor in a series of experiments against a smoldered Marlboro Medium Cigarette and found that the PPAH tracked the cigarette's secondhand smoke respirable particle (SHS-RSP) emissions closely. Repace (2003) found about a 2000:1 ratio between SHS-RSP and SHS-PPAH mass emissions in field studies in 8 hospitality venues in the State of Delaware. In order to further calibrate the EcoChem PAS2000CE, an experiment was conducted using a human smoker smoking a Marlboro Lite 100s cigarette as described below.

The basic purpose of the original experiments described in this paper is to conduct an indoor/outdoor survey of PPAH in the relatively clean environment of a cruise ship at sea in the South Atlantic Ocean where diesel exhaust from automobiles is non-existent. A gas-powered turbine ship, the Summit operated by Celebrity Lines out of Fort Lauderdale, Florida was selected, and measurements were conducted in February 2004. 3 sets of experiments were conducted: A calibration experiment, and measurements of indoor and outdoor PPAH on 2 separate days in various parts of the ship.

Experiment 1. Calibration of the EcoChem PAS2000CE against a Marlboro Lite 100s Cigarette smoked by a human smoker in a cruise ship stateroom.

The PPAH monitor was deployed in indoor nonsmoking areas of the ship (including the stateroom) 15 minutes prior to and 15 minutes subsequent to the smoking experiment to obtain a PPAH background. The cigarette was lit using a match, and smoked by a 50-yr old female heavy smoker who volunteered. The 28 cubic meter stateroom 2169 on Deck 2, an inside stateroom, was occupied by the smoker and her spouse during the experiment. The PPAH monitor was placed in the middle of room on the stateroom bed, and the smoker sat on the bed about 4 feet from the monitor. Figure 1 shows the growth and decay of PPAH from smoking and the before-and-after background levels. Figure 2 gives an analysis of the decay curve, from which the effective air exchange rate for concentration decay (removal by air exchange plus absorption on room surfaces) is calculated. The decay rate is calculated from the slope of the decay curve at 6.63 air changes per hour (h^{-1}). The growth plus decay curves had 28 data points, i.e., N = ~28 min; for the decay curve only, N = 22 min, and non-SHS background was 2.36 nanograms per cubic meter (ng/m^3).

CONTROLLED EXPERIMENT OF PPAH EMISSIONS IN A STATEROOM

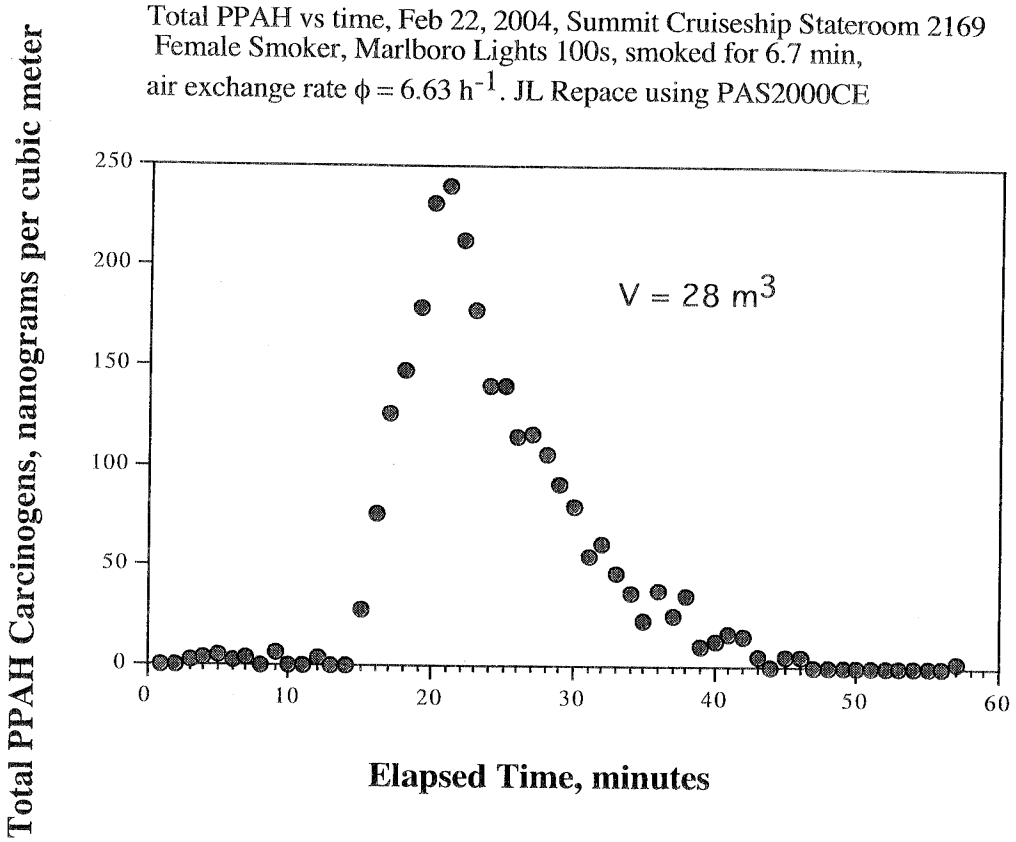

Figure 1. PPAH emissions before, during, and after a Marlboro Cigarette was smoked by a human smoker for 6.7 minutes in an inside stateroom on a cruise ship, consuming 0.55 g of tobacco.

After smoking, the cigarette butt was extinguished in water, dried overnight, and bagged. A second unsmoked cigarette from the same pack was obtained and also bagged for later measurement. Subsequent to the cruise, the unsmoked cigarette and smoked cigarette butt were weighed 3 times each to 4 decimal places on a Mettler AE240 Digital Electronic Balance, weighing in at 0.983 grams (g) and 0.429 g respectively, after being conditioned overnight, for an estimated net amount of tobacco combusted of 0.554 g. The cigarette filter alone weighed 0.258 g, leaving the net amount of tobacco at (0.983-0.258) = 0.725 g. The PPAH emissions are calculated as follows: From the decay curve (Fig. 2), the maximum concentration attained at the point of extinction of the cigarette i.e., the cigarette smoking time (t_s = 6.7 min) is $\mathbf{X}_{max}$ = 298 ng/m^3. The growth curve is given by the equation:

$$\mathbf{X}_{max}(t_s) = (g_c/\omega)\{1 - e^{-(t/\tau)}\} \text{ (Equation 1),}$$

where g_c is the PPAH emission rate in ng/min, $\omega = \phi V$ is the product of the air exchange rate ϕ in air changes per hour (h^{-1}), and the space volume V (m^3) which is the clearance rate or rate at which a unit volume of air is cleaned of PPAH by removal processes (m^3/hr). Thus, the unit emission rate of PPAH in ng per gram of tobacco burned is given by G/M_b, where $G = g_c t_s$ in units of ng, and M_b is mass of tobacco burned in grams (g). Solving equation (1) for g_c, multiplying both sides of the equation by t_s and equating the result to G yields, for values of the parameters: $V = 28$ m^3; $t = t_s = 6.7$ min; $\phi = 6.63$ h^{-1}; $M_b = 0.554$ g; $X_{max} = 298$ $\mu g/m^3$, $\tau = 1/\phi = 9.05$ min, $\omega = 185.64$ m^3/h; $g_c = 1.763$ μg PPAH/min, and the mass emissions of PPAH from the Marlboro Lite 100 cigarette smoked by a human smoker are:

$$G = g_c\, t_s = (\omega \mathbf{X}_{max} t_s)/\{1 - e^{-(t/\tau)}\} = 21.22\ \mu g/g.$$

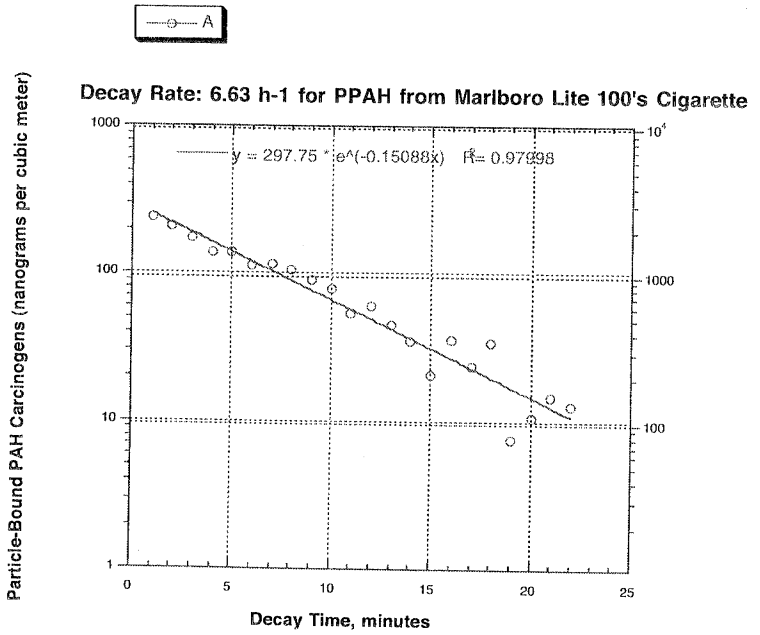

Figure 2. Semi-log plot of PPAH decay vs time for Figure 1, Marlboro Lite 100 Cigarette in a cruise ship stateroom. Background-subtracted decay curve $N = 22$ min.

The Marlboro Lite 100 cigarette measures 10 cm, where the filter occupies 3 cm, leaving 7 cm of tobacco. 1.5 cm of this cigarette was not smoked, leaving 1.5 cm (0.554 g/5.5 cm) = 0.151 g of tobacco unsmoked. Thus, the fully-smoked cigarette is estimated to burn (0.554 + 0.151) = 0.705 g of tobacco, to burn for (0.705/0.554)(6.7 min) = 8.5 min, and to emit G_c = (21.22)(0.7g) = 14.85 μg of PPAH per cigarette when smoked by this smoker.

Repace (2003) found an ETS RSP-to-ETS PPAH ratio of ~2000:1 in his Delaware Air Quality survey; based on this ratio, and the 25.4 billion cigarettes smoked in California (CARB, 2003 p. IV-1) in 2002, an estimated (21.22 μg/g)(0.7 g/cigarette)(25.4 x 10^9 cigarettes) = 377 kilograms of PPAH emitted into California air annually in 2002.

INDOOR/OUTDOOR PPAH MEASUREMENTS ON A CRUISE SHIP

The EcoChem PAS 2000CE real-time PPAH monitor was deployed discretely about the ship while underway at sea in a variety of smoking (SM) and nonsmoking (NS) microenvironments, including a stateroom (7200, NS), restaurant (Cosmopolitan, NS), ship corridors (SM & NS), a bar on the swimming pool deck (SM), a bar on the aft deck at which cigar, pipe, and cigarette smoking was permitted 8:30-midnight (SM). As a NS outdoor control, areas in the forward part of the ship distant from smoking were measured. Two sets of measurements were performed 6 days apart. The EcoChem PAS 2000CE's clock and a Pulsar quartz crystal wristwatch with a sweep second hand were synchronized to a laptop computer referenced to a Seiko atomic clock. A time-activity pattern diary was kept in order to identify microenvironments visited in the recorded data.

These averages of the microenvironmental data measured are shown in Tables 1 and 2. In two cases, entries are presented with and without outliers removed in order to assess true NS backgrounds in the absence of ETS, reflected in reductions in peak concentrations, e.g., intrusion into Stateroom 7200 from smoking on other balconies, and smoke from extinguished birthday candles on several cakes. Table 3 describes the occupancy of various areas of the ship and gives pertinent dimensions.

Table 1. Indoor/outdoor PPAH levels in nanograms per cubic meter (ng/m^3) on a cruise ship in the presence and absence of smoking. Sunday, Feb. 15, 2004, at sea (unless otherwise specified, the number of active smokers refers to burning cigarettes only).

Microenvironment	Mean PPAH (SD)	Mean # of active smokers	Number of 1-min data points	Range	Ratio to Outdoor Nonsmoking
Outdoor Deck 11 Nonsmoking	2.62 (2.9)	0	58	0-13	1.00
Deck 4 Restaurant (NS)	2.69 (2.4)	0	130	0-11	1.03
Stateroom 7200	7.00 (18)	0	41	0-115	2.67
Stateroom 7200[a]	4.30 (3.0)	0	40	0-11	1.64
Ship Corridors	6.22 (10)	NR	40	0-49	2.37
Cigar Bar Outdoors C=cigars Breezy	8.45 (12)	**2.9 (1.61) C: 3.8 (0.1) Pipe-1 (0)**	60	0-81	3.23
Deck 10 Pool Bar Outdoors, Forward	8.91 (12)	1.87 (1.6)	45	0-60	3.40

[a]Outlier removed: probably due to smoking on adjacent balcony; NR = not recorded

Table 2. Indoor/outdoor PPAH levels in ng/m^3 on a cruise ship in the presence and absence of smoking. Sunday, Feb. 21, 2004, at sea (unless otherwise specified, the number of active smokers refers to burning cigarettes only).

Microenvironment	Mean PPAH (SD)	Mean # of active smokers	Number of 1-min data points	Range	Ratio to Outdoor Nonsmoking
Outdoor Deck 11 Nonsmoking*	3.96 (2.49)	0	27	0-8	1.00
Deck 4 Restaurant (NS)	8.44 (29)	0	59	0-197	2.13
Deck 4 Restaurant (NS)[a]	2.35 (2.6)	0	55	0-13	0.59
Stateroom 7200	3.11 (2.91)	0	71	0-18	0.78
Ship Corridors	5.44 (4.9)	NR	39	0-19	1.37
Cigar Bar Outdoors, Light wind; C=cigars	9.95 (8.96)	**1.62 (0.52) C: 1.4 (0.52)**	42	0-48	2.51
Deck 11 Bar Outdoors, Forward	11.12 (11.66)	**1.0 (0) C: 1 (0)**	16	3-52	2.81
Casino	10.71 (10.18)	2.2 (2.4)	76	0-54	2.70
Outdoors Smoking	8.60 (13.56)	1.33 (0.82)	25	0-58	2.17

*[a]Outliers removed:likely due to birthday cake candle smoke; *possibly biased upwards by proximity to door; NR = not recorded*

RESULTS

Environmental: Measurements of PPAH were made on a 91,000 ton cruise ship of length ~965 feet, and beam 106 feet. The ship has a maximum speed of 24 knots, and is powered by "environmentally sensitive smokeless gas turbines". It has 11 decks and 10 elevators communicating among those decks. It is capable of holding 1960 passengers and a crew of 999, and has

1091 staterooms. A picture may be viewed at: http://www.my-celebrity-cruises.com/celebrity-cruises/summit.htm.

The environmental conditions during the Feb. 15th measurements described in Table 1 were: partly cloudy, 26°C, 76% RH, barometer 1019 mb., wind SE at 20 knots @4:45 PM Atlantic time, and the location was above the Puerto Rico Trench in the South Atlantic. Measurements were conducted episodically from 4:45 PM to midnight. For Table 2, environmental conditions during the Feb. 21st measurements were: partly cloudy, 25.6°C, 76% RH, barometer 1019 mb., wind 10-15 knots @12:46 PM Atlantic time, and the location was above the Silver Bank Passage in the South Atlantic. Measurements were conducted episodically from 12:45 PM to midnight.

Physical: Outdoors, the port side of the ship is the smoking-permitted side, and all smoking measurements were made on that side; the starboard side of the ship is nonsmoking. Deck 11 is the jogging deck and is, essentially mostly open to the air on its perimeter and in a 100 ft by 150 ft central deck open above and on both long sides, the superstructure of the ship occupying the remainder of the fore-and-aft dimensions. Deck 10 is the pool deck, which is enclosed on 4 sides, but which has large operable windows on both long sides, which were mostly open. Deck 10 has a 12 ft high canopy on all 4 sides, but communicates with the large pool area of approximate dimensions 80 ft by 150 ft, which is open to the sky. The Deck 11 bar has an ~10 ft high canopy extending about 8 ft beyond the edge of the bar but is otherwise open on 3 sides to the air. The cigar bar area is ~105 ft wide by 24 ft deep, and has a 12 ft canopy over the center covering about a third of the deck width in front of the bar, with a higher ~18 ft canopy over the bar area, and individual umbrellas over all tables not under the main canopy. This area has a wall and doors on the bar side, but otherwise is open on 3 sides to the air and is located on the stern of the ship. The Deck 10 pool bar smoking area, is tucked in the forward corner of the pool deck and is covered by the canopy and abuts a wall on its backside. Outdoor measurements, except for the cigar bar, were made during the daylight hours at times of normal occupancy. The cigar bar was open only from 8:30 PM to midnight; although measurements were made on the port side, smoking occurred on both sides. In all of these outdoor locations, wait staff, bartenders, and musicians were exposed.

Indoors, only the port corridors were smoking permitted, and measurements were made in both port and starboard corridors. In the casino, the port side was smoking, but this was not always respected, and one end of the casino contained a bar area. Two sets of measurements in the casino area were made, one made in the early evening (8.7 ng/m^3 ave.) and one in the late evening (14.6 ng/m^3); all data were combined and averaged (10.7 ng/m^3) as presented in Table 2. In the casino and other indoor locations, dealers, wait staff, bartenders, and musicians were variously exposed.

PPAH: PPAH levels in the indoor casino averaged 10.71 ng/m^3. This is comparable to both the outdoor Deck 10 (8.9 ng/m^3) and Deck 11 (11.12 ng/m^3) Bars and the Cigar Bar (9.95 ng/m^3) concentrations and the outdoor smoking (8.6 ng/m^3) results as shown in both Table 1 and Table 2. This suggests that despite these areas being outdoors, the effect of strong breezes and significant open areas is insufficient to dilute the PPAH concentrations to background levels. Figure 3 illustrates the data recorded by the PAS2000CE before, during, and after the cigar bar visit described in Table 1, and Figure 4 summarizes the results for all microenvironments.

Table 3 further characterizes the locations sampled.

Table 3. Capacity of Public and Private Cruise ship Areas in which PPAH were measured.

Location	Capacity, Persons	Area	Volume
Stateroom 2169	2	-	28 m^3
Deck 4 Restaurant (NS)	1170	-	-
Stateroom 7200	2	-	36 m^3
Cigar Bar Outdoors, Aft	~105	2155 ft^2	12 ft partial overhead canopy
Deck 11 Bar Outdoors, Forward	~25	-	10ft partial canopy open to air 3 sides
Casino Indoors	270	5292 ft^2 (ceiling ht. 8.583')	1286 m^3
Outdoors Deck 10 Smoking Port Side	~325	-	12 ft overhead canopy; in corner of pool area

Finally, the controlled experiment showed that the cigarette when smoked by a human smoker is similar to results reported by Rogge et al. (1994), but has a much larger emission factor relative to those carcinogenic PPAH emissions reported for SS alone in the literature (Table 4) perhaps due to the contribution of exhaled MS smoke to the SHS, or to differences in the PPAH emissions relative to machine-smoked 1R4F research cigarettes.

Although measurements were conducted on a Celebrity Lines ship, the author has taken cruises previously on Holland America and Princess Lines ships of a similar nature; it is likely that levels of SHS on those ships were similar.

Table 4. Carcinogenic PPAH, IARC Status, Amount in Cigarette Smoke*

Particulate Phase PAH (PPAH)	IARC Carcinogen In Lab Animals (a) Humans (h)	Amount Measured In Mainstream Smoke (MS) (ng/cig)	Amount Measured in Sidestream Smoke (SS) or SHS (ng/cig)*	Reference*
Benz(a)anthracene	Sufficient[a]	20-70	412	*A,B*
Benzo(b)fluoranthene	Sufficient[a]	4-22	132	*A,B*
Benzo(j)fluoranthene	Sufficient[a]	6-21	32	*A,B*
Benzo(k)fluoranthene	Sufficient[a]	6-12		*A*
Benzo(a)pyrene	Sufficient[a,h]	20-40	74	*A,B*
Dibenzo(a,i)pyrene	Sufficient[a]	1.7-3.2		*A*
Dibenz(a,h)anthracene	Sufficient[a]	4		*A*
Dibenzo(a,l)pyrene	Sufficient[a]	present		*A*
Indeno(1,2,3-cd)pyrene	Sufficient[a]	4-20	51	*A,D*
5-methylchrysene	Sufficient[a]	0.6		*A*
All PPAH in SS machine-smoked 1R4F Univ. of KY research cigarette	-	-	1,067	*B*
All PPAH in SHS + Exhaled MS human-smoked Camel, Merit, Winston, Benson & Hedges cigarettes	-	-	13,500	*C*
All PPAH SHS + Exhaled MS human-smoked Marlboro Lite 100s	-	-	14,850	*This Experiment*

*References: *A*. Hoffmann & Hoffmann (1998); *B*. Gundel et al. (1995); *C*. Rogge et al. (1994); *ng/cig = nanograms per cigarette. Blank cells indicate no data available; IARC = International Agency for Research on Cancer. *D*. Hecht (2004).

Table 4 also shows that many of the chemical compounds in PPAH from cigarette smoke MS, SS, and SHS are known animal or human carcinogens

whose presence has been quantified. Several of the individual PPAH compounds listed in Table 4 have been measured in indoor atmospheres at levels ranging from 0.3 to 2 ng/m^3 (Hecht, 2004). Repace (2003a,b) has measured average levels of PPAH inside a total 14 hospitality venues, 6 in Boston, MA and 8 in Wilmington, DE, ranging respectively from 6 to 249 ng/m^3, in the presence of smoking, and averaging about 5 ng/m^3 in the absence of smoking.

Discussion: Why should outdoor SHS levels be non-trivial in view of the large dilution volumes and the strong breezes attendant for a cruising ship at sea? As Repace (2000) has suggested, individual cigarettes are point sources of air pollution; smoking in groups becomes an area source. Outdoor air pollutants from individual point sources are subject to plume rise if the temperature of the smoke plume is hotter than the surrounding air; however if the plume has a small cross-section, as for a cigarette, it will rapidly cool and lose its upward momentum, and then will subside as the combustion particles and gases are heavier than air. Thus, in the case of no wind, the cigarette plume will rise to a certain height and then descend, and for a group of smokers, even on a cruise ship, their smoke will tend to saturate the local area with SHS. In the case where there is wind, the amount of thermally-induced plume rise is inversely proportional to the wind velocity -- doubling the wind velocity will halve the plume rise. In this case, the cigarette plume will resemble a cone tilted at an angle to the vertical. The width of the cone and its angle with the ground will depend upon the wind velocity: a higher wind will create a more horizontal cone, a smaller cone angle, and a higher concentration of SHS for downwind nonsmokers. If there are multiple cigarette sources, the downwind concentrations will consist of multiple intersecting cones, i.e., overlapping plumes. As the wind direction changes, SHS pollution will be spread in various directions, fumigating downwind nonsmokers.

Should we be concerned about a tripling of the PPAH level exposure? According to the Agency for Toxic Substances and Disease Registry (ATSDR, 2003), "animal studies have shown that PAH exposure increased the rate of birth defects in test animals, and reduced their ability to fight disease, even after short-term exposure. It is not known whether these effects occur in people. However, people exposed to PAHs for prolonged periods have developed cancer. Animal studies have demonstrated that some PAHs have caused lung cancer, stomach cancer, and skin cancer." Ten carcinogenic particulate-phase PAHs have been identified in tobacco smoke as listed in Table 4; this is one-sixth of known tobacco smoke

carcinogens (Hecht, 2004; Hoffmann and Hoffmann, 1998). The data collected here suggest that wait staff, bartenders, and service personnel, as well as nonsmokers frequenting smoking areas such as outdoor cafes in California will suffer increased exposure to PPAH which represent only $1/6^{th}$ of the 69 carcinogens in SHS by number. Given the workplace smoking ban for indoor California workplaces, outdoor microenvironments such as cafes, bars, and restaurants, remain the only locations where carcinogenic occupational SHS exposure remains.

Conclusions:

1. From an experiment using a human smoker, it appears that Marlboro Lite 100s cigarettes emit ~15 micrograms of carcinogenic PPAH per cigarette, or 22 micrograms per gram of tobacco smoked. This emission is in agreement with a California study reported for human smokers in the literature using chemical analytical methods. Peak PPAH levels after 6.6 minutes of smoking were elevated >100 times background.

2. Based on the controlled experiment using a Marlboro Lite 100 cigarette conducted here, cigarette smoking alone emits an estimated 377 kilograms of PPAH into California air annually at 2002 levels of smoking.

3. Measurements of PPAH outdoors on a cruise ship show levels are tripled by secondhand smoke relative to either outdoor or indoor nonsmoking areas, suggesting that secondhand smoke does not disperse well even in breezy outdoor areas where smokers congregate.

4. Measurements of outdoor PPAH levels in the presence of smoking on a cruise ship are comparable to levels measured in the popular cruise ship casino during smoking.

5. SHS is measurable at sufficiently-elevated levels in well-ventilated outdoor environments with unlimited volume of dispersion to be of concern, posing a carcinogenic threat to nonsmokers, especially waiters, musicians, and bartenders, who suffer long-duration occupational exposures.

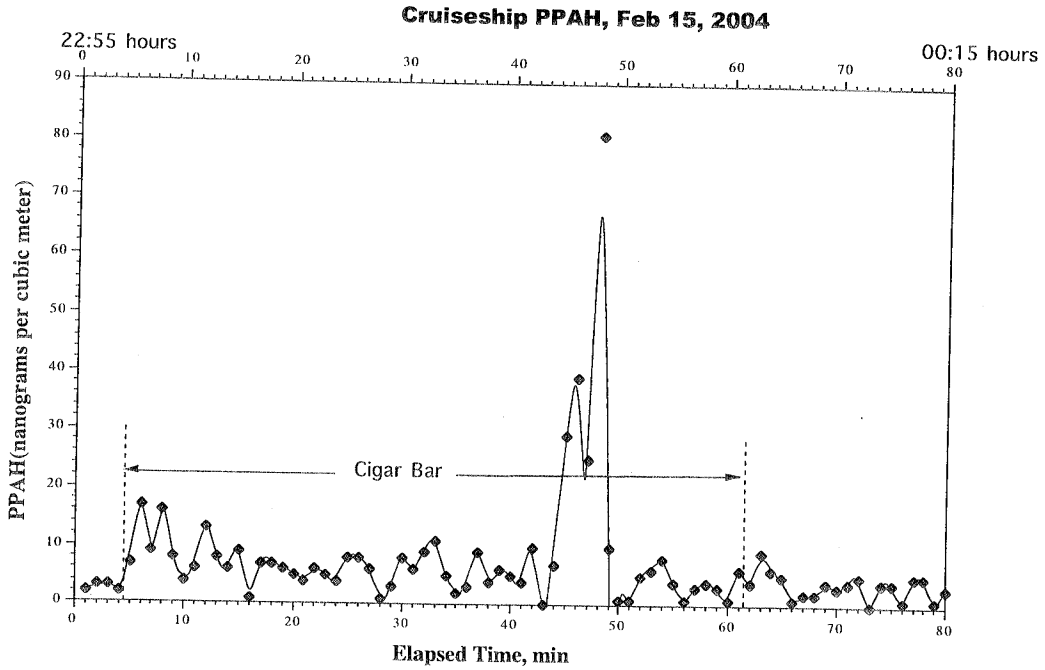

Figure 3. PPAH vs. time data. The clocktime recorded by the PAS2000CE monitor is converted into elapsed time for plotting purposes. The period shown is before, during, and after the Feb. 15 visit to the outdoor cigar bar during breezy conditions as described in Table 1. The large peak between 43 and 49 minutes is ~40 times background, and is a proximity peak due to a cigarette smoker placing her cigarette unbidden on an ashtray at our table while she was dancing. This PPAH peak is illustrative of the increased exposure concentration which might be experienced continually by a nonsmoking waiter, bartender, musician, or a fellow patron sitting in an outdoor café at a table with a smoker. The periods preceding and following the visit to the cigar bar were inside the ship's corridors and stateroom 7200.

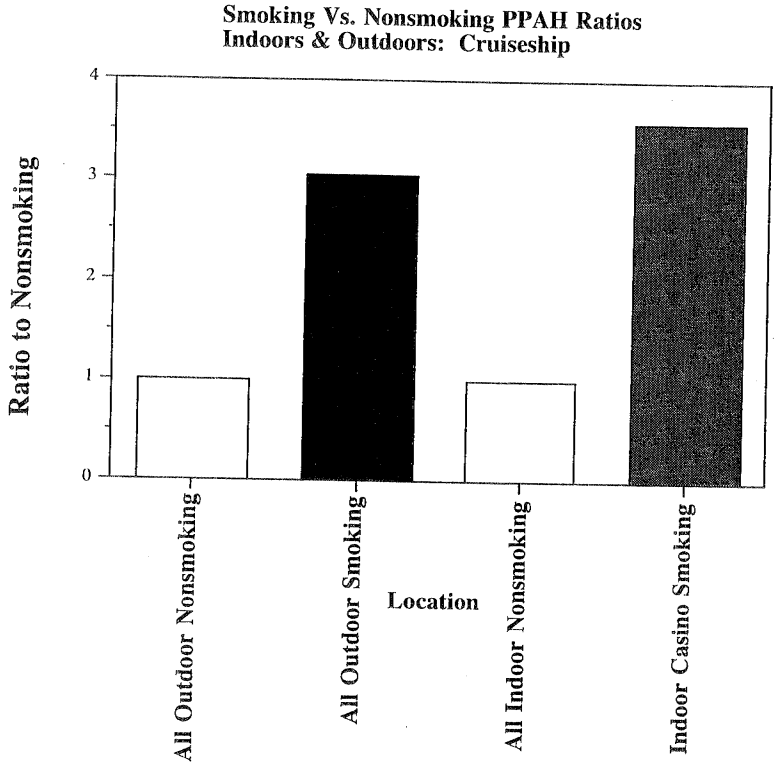

Figure 4. Weighted-mean ratios for all Outdoor Nonsmoking measurements to all Outdoor Smoking measurements, versus ratios of all Indoor Nonsmoking measurements to all Indoor Smoking measurements. Outdoor smoking on a cruise ship can expose nonsmokers to PPAH levels comparable to those in an indoor casino, suggesting that outdoor carcinogen exposures of nonsmokers from secondhand smoke are not low.

Acknowledgement: This work is supported by the Flight Attendant Medical Research Institute. The author is grateful to HM Repace for on-board logistical support and for cigarette mass measurements.

References

ATSDR. Agency for Toxic Substances and Disease Registry. ToxFAQs for Polycyclic Aromatic Hydrocarbons (PAHs). http://www.atsdr.cdc.gov/tfacts69.html.

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY. (2003). *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant.* Office of Environmental Health Hazard Assessment.

Chuang JC, Callahan PJ, Lyu CW, Wilson NK. Polycyclic aromatic hydrocarbon exposures of children in low-income families. Journal of Exposure Analysis and Environmental Epidemiology 2:85-98 (1999).

Danissenko MF, Pao A, Tang M-s, Pfeifer G. Preferential formation of benzo(a)pyrene adducts at lung cancer mutational hotspots in P53. Science 1996; 274, 430-432.

Glantz SA, Parmley WW. Passive smoking and heart disease. Circulation 1991; 83: 1-7.

Gundel LA, Mahanama KRR, Daisey JM. Semivolatile and particulate aromatic hydrocarbons in environmental tobacco smoke: cleanup, speciation, and emission factors. Environmental Science and Technology 29:1607-1614 (1995).

Hart KM, McDow SR, GiegerW, Seiner D, Burtscher H. (1993). The correlation between in situ real-time aerosol photoemission intensity and particulate polycyclic aromatic hydrocarbon concentration in combustion aerosols. Water, Air, and Soil Pollution 63:75-90.

Hecht SS. Carcinogen derived biomarkers: applications in studies of human exposure to secondhand tobacco smoke. Tobacco Control 2003; 13: i48-i56.

Hoffmann D and Hoffmann I. Chemistry and Toxicology. Ch. 3, In: *Smoking and Tobacc Control Monograph 9. Cigars - Health Effects and Trends.* National Institutes of Health, National Cancer Institute, Bethesda, MD (1998).

Hoffmann D and Hoffmann I. Significance of exposure to sidestream tobacco smoke. Ch. 1, in *IARC Scientific Publications no.81, Environmental Carcinogens--Selected Methods of Analysis--Volume 9 Passive Smoking; O'Neill I, Brunnemann K, Dodet B, and Hoffmann D.* International Agency for Research on Cancer, World, Health Organization, United Nations Environment Programme, Lyon, France; 1987.

McBride SJ, Ferro AR, Ott WR, Switzer P, :Hildemann LM. Investigations of the proximity effect for pollutants in the indoor environment. J Exposure Analysis & Environmental Epidemiology (1999) 602-621.

McDow SR, Giger W, Burtscher H, Schmidt-Ott and Siegmann HC (1990). Polycyclic aromatic hydrocarbons and combustion aerosol emission. Atmospheric Environment 24A, 2911-2916.

Ott WR, Wilson NK, Klepeis N, Switzer P. Real-time monitoring of polycyclic aromatic hydrocarbons and respirable particles from environmental tobacco smoke in a home. Proc. International Symposium, Measurements of Toxic and Related Air Pollutants, Air & Waste Management Association, Durham, NC, May 3-6, 1994. NTIS PB-94-RO9756.

Ott WR, Repace JL. Poster. Modeling and Measuring Indoor Air Pollution from Multiple Cigarettes Smoked in Residential Settings. International Society for Exposure Analysis, Stresa, Italy.

Repace JL. Banning outdoor smoking is scientifically justifiable. Tobacco Control 9:98 (2000).

Repace JL. Poster, Secondhand Smoke in the Hospitality Industry: Indoor Air Quality Before & After a Smoking Ban, 13th Annual Conference, International Society for Exposure Analysis, Stresa, Lago Maggiore, Italy.

Repace JL, Ott WR, and Klepeis NE. Indoor Air Pollution from Cigar Smoke. In: *Smoking and Tobacco Control Monograph 9. Cigars - Health Effects and Trends.* National Institutes of Health, National Cancer Institute, Bethesda, MD (1998).

Rogge WF, Hildemann LF, Mazurek MA, Cass GR. Sources of fine organic aerosol. 6. Cigarette smoke in the urban atmosphere. Environmental Science & Technology 26:1375-1388(1994).

Siegmann H, Ott W. Using multiple continuous fine particle monitors to evaluate tobacco, incense, cooking, wood burning, and vehicular sources in indoor, outdoor and in-transit settings. (in preparation).

Zhiqiang Q, Siegmann K, Keller A, Matter U, Scherrer L, Siegmann HC. Nanoparticle air pollution in major cities and its origin. Atmospheric Environment 34:443-451 (2000).

A response to:
California Air Resources Board
Proposed identification of Environmental Tobacco Smoke as a Toxic Air Contaminant
November 2003, Public Review Draft

Part B: Health Effects

New developments since the last evaluation in 1997:

Missing from all studies on the purported harmful effects of tobacco use on morbidity and mortality, is an analysis of the confounding influence of exposure to Adverse Childhood Experiences (ACE's) and of the stress of the Anti-tobacco program itself.

Background: In this series of studies, ACE's, being exposed to child abuse or household dysfunction had a graded influence on a host of risky behaviors including tobacco use, alcohol and drug abuse, paternity and teen pregnancy, depression, attempted suicide and eating disorders. ACE's also have an independent, graded effect on mortality. Feletti acknowledges that Nicotine may have beneficial psychoactive effects regulating affect, and mood, consequences of depression. Nicotine is well known for reducing stress and increasing attention span. Does tobacco use really cause stress related heart disease? Or is tobacco use simply a marker for stress? Unfortunately, the article, does not present the intercorrelations between ACE's, tobacco use and mortality. This would be a difficult model, but is still significant by its absence. We would not expect that the stress of exposure to ACE's to effect (non-stress related) cancers of the respiratory system. However, stress in implicated in <u>every</u> other illness attributed to tobacco use.

The confounding influence of ACE's as it applies to maternal smoking and Fetal Growth and Preterm Delivery (FG&PtD), including BW, LBW, IUGR, SGA.

Several studies have included some of the measures of stress: adverse adult life experiences, trait anxiety, current stress, and domestic violence during pregnancy. However, none have measured the entire range to include ACE's.

A case control study of partner abuse and LBW (Campbell 1999) found that < 15 pound weight gain, spousal abuse and smoking during pregnancy was associated with LBW in full term infants, but only < 15 pound weight gain was related in preterm infants. Smoking was not included in the final adjusted model(assuming that it did not influence the final model). Stress (Daily Hassles Scale) was associated with abuse, but not LBW. The author suggests that "Abuse may be one of a cluster of difficult life experiences that affect birth weight"

One interesting (n=1861) Urban prospective study (Orr 1996) of psychosocial stressors and LBW found that African Americans have a higher rate of LBW and correlation with Moderate/High Stressors and hypertension, whereas the Caucasian population has a lower rate of LBW which is more highly correlated with hypertension, low pre-pregnancy weight, smoking and drug use.

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The prevalence of high levels of stressors and established risks (including smoking) in this study was similar in both races. Yet, the risk (odds ratio) for smoking is 6.89 for Caucasians and 1.57 in African Americans. Smoking is a greater risk factor for LBW for Caucasians than it is for African Americans? How can this possibly be?

Table 1

	Caucasian n= 428 LBW= 32		**African-American** n=1433 LBW=156	
	P-value	Odds Ratio	P-value	Odds Ratio
Moderate/High Stressors	.10	.48	.03	1.52
Low Pre-pregnancy Weight	.17	2.29	.005	2.13
Hypertension	.002	15.11	.02	2.93
Smoking	.002	6.89	.03	1.57
Drug Use	.05	2.95	.18	1.48

Table 2

	Caucasian	**African-American**
LBW rate (1990/1995)	5.7/6.22	13.25/13.13
Smoking rate (1990/1995)	23.5/23.4%	20.8/23.5
Decrease in Smoking rate (1990/1995)	.4%	- 13%
Smoking/preg rate (1990/1995)	19.4/15.0%	15.9/10.6%
Decrease in Smoking/preg rate (1990/1995)	22.6%	33.3%

Health, United States, 2003 Trend Tables (tables 10,12,59)
http://www.cdc.gov/nchs/products/pubs/pubd/hus/03hustop.htm

From 1990 to 1995 smoking rates in the US for African American females increased, pregnant African American females decreased 33% as compared to 22.6% for Caucasians(Table 2). One would have to assume that pregnant females in the US were especially targeted with anti-smoking programs, with African American females getting the extra heavy dose. During this time, there was no significant decrease in the rate of LBW(Table 2). Recognizing that those who do quit are the easy ones, with a low Nicotine Tolerance score and associated risks for tobacco related illnesses anyway, one would have to question the utility of the anti-smoking program in the first place.

The author speculates that "a minority group, traditionally suffering exploitation and discrimination, may react differently to stressors than their Caucasian counterparts." Indeed, this may be because of an increase in genetic susceptibility over several generations. It may also be because of the (cumulative) effect of stressors that were not identified in the Prenatal Social Environment Inventory (PSEI) survey instrument. The author made it a point to include measures of chronic stressors (during the past 12 months) that were unique to African American culture. This apparently lowered their odds ratio for smoking to a paltry 1.57 that, while still "significant", is still highly subject to unknown confounding factors, such as ACE's, partner abuse, and exposure to heavy doses of anti-tobacco messages.

Stress can be mitigated by periods of down time: social support, security, economic prosperity, and sated sleep. For black females, typically raising families alone, this is especially problematic. Societies help too often involves sending critical messages, marginalizing those who appear outside the norm. So, we have an at risk population that has suffered exploitation, and discrimination because they are black and female and now because they smoke. We as a society have come so far, and yet, still such a long distance to go.

As it applies to studies of pregnant non-smoking spouses of smokers (ETS):
Refer to Chapter 3. Developmental Toxicity - 1. Perinatal Manifestations
3.2 Fetal Growth and Preterm Delivery

None of the studies of ETS and FG&PtD have included ACE's in the parents. Those who are exposed to ACE's are more likely to smoke. The presence of measures of ETS (Cotinine) in the mother (or child) even though she does not actively smoke may be a marker for exposure to ACE's in the mother or because of assortive mating(discussed below), in the biological father who smokes. Either biological parent may transfer the genetic risk for FG&PtD. The father, because he smokes and is at increased risk for ACE's, may also be at increased risk for spousal abuse during pregnancy, another risk factor for FG&PtD. Paternity is a marker for ACE's also an issue. The same would apply to biological relatives living in the home.

As it applies to studies of infants of non-smoking spouses of smokers (ETS):
Refer to Chapter 4. Developmental Toxicity - II. Postnatal Manifestations
4.1 Sudden Infant Death Syndrome (SIDS)

None of the studies of ETS and SIDS have included ACE's in the parents. The same analysis as above applies.

Animal Models
Animal are not reliable models of human exposure. In all studies that I am aware of, animals do not select to use tobacco (nicotine). Humans do choose actions to preserve and enhance life. Tobacco has been in use for 2000 years. Those who smoke are not dying off in their 20's.

Biomarkers of Exposure

Is it the Nicotine? Well, as it turns out, there is no Nicotine in ETS. Cotonine, one of the metabolites of Nicotine can be measured as a proxy. Is it Benzene or Vinyl Chloride (Table 7-4D). Both are identified as carcinogens by the IARC. There has not been any identification as to exactly which of the purported harmful constituents causes the specific illnesses or conditions associated with exposure to ETS. In fact, if the particular constituent could be identified, the manufacturing process could be changed to eliminate the harmful constituent.

There is no safe exposure? If you apply this idea to the extreme, it implies that any exposure to ETS is harmful. In other words, a person smoking in Los Angeles could theoretically effect the health of someone in Washington, DC. Of course, this is ludicrous. Unless the specific constituent of tobacco is identified, and the exact amount and time exposure required (not just the risk) to cause cancer, then it would be improper to regulate it as toxic.

Assortive Mating

A recent letter(Willensen 2003) commenting on a study(Price 2003) of spousal similarities found that "assortative mating should not be hastily dismissed as a cause for spouse similarities in disease". Part of the risk for cancer is genetic susceptibility. The spouse, through assortment for these factors (including ACE's) is based on similarity at the time dating began, is likely to have an increased risk for these same factors.

The social effects of ACE's, stress and the Anti-tobacco program

ACE's and the resultant stress have a cumulative effect, especially on the neuro-hormonal, fight or flight system. Time, social support, and a good nights sleep will help recover from stress. Too much unresolved stress leads to post traumatic stress syndrome and aberrant behavior. An individual from a dysfunctional family with few resources has an uphill battle. This at-risk population has already been exposed to more than their share of dysfunctional authority figures and in extreme cases, actual child abuse. Characteristic of this experience is the use of excessive control, distorted guilt, marginalization, and copious punishment. Survivors of these challenging childhoods are all too often mistaken for easy targets for exploitive behavior.

The current cessation programs rely heavily on the use of distorted blame, social ostracization and punishment in the form of job discrimination and exorbitant taxes. The anti-tobacco program forces a choice between two paths, both with negative consequences. It simply produces conflict and adds ....more stress, to those at greatest risk. This unproductive stress increases illness. No study to date has evaluated the extent of this unintended program effect. This thorough analysis needs to be done, especially in the stress sensitive pregnant women (Relier 2001,Meyers 1977) and those exposed to high levels of trauma and stress in the Military/Veteran (Hourani, 1999) populations. Much more effective cessation methods need to be offered, long before health care spends money on programs that appear to continue and institutionalize the dysfunctional relationship that many were exposed to in their youth.

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References:

Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, et al.
Adverse Childhood Experiences and Smoking During Adolescence and Adulthood
JAMA. 1999;282:1652-1658

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS
Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study.
Am J Prev Med 1998 May;14(4):245-58

Relier JP.
Influence of maternal stress on fetal behavior and brain development.
Biol Neonate 2001 Apr;79(3-4):168-71

Shalev E, Eran A, Harpaz-Kerpel S, Zuckerman H.
Psychogenic stress in women during fetal monitoring (hormonal profile).
Acta Obstet Gynecol Scand 1985;64(5):417-20

Myers RE.
Production of fetal asphyxia by maternal psychological stress.
Pavlov J Biol Sci 1977 Jan-Mar;12(1):51-62

Campbell J, Torres S, Ryan J, King C, Campbell DW, Stallings RY, Fuchs SC.
Physical and nonphysical partner abuse and other risk factors for low birth weight among full term and preterm babies: a multiethnic case-control study.
Am J Epidemiol. 1999 Oct 1;150(7):714-26.

Orr ST, James SA, Miller CA, Barakat B, Daikoku N, Pupkin M, Engstrom K, Huggins G.
Psychosocial stressors and low birthweight in an urban population.
Am J Prev Med 1996 Nov;12(6):459-466

Willemsen G, Vink JM, Boomsma DI.
Letter - Assortative mating may explain spouses' risk of same disease
BMJ 2003;326:396 (15 February)
http://bmj.bmjjournals.com/cgi/content/full/326/7385/396/a#Fu1

Price RA, Vandenberg SG.
Spouse similarity in American and Swedish couples.
Behav Genet 1980; 10: 59-71

Relier JP.
Influence of maternal stress on fetal behavior and brain development.
Biol Neonate 2001 Apr;79(3-4):168-71

Myers RE.
Production of fetal asphyxia by maternal psychological stress.
Pavlov J Biol Sci 1977 Jan-Mar;12(1):51-62

Hourani LL, Yuan H, Bray RM, Vincus AA.
Psychosocial correlates of nicotine dependence among men and women in the U.S. naval services.
Addict Behav. 1999 Jul-Aug;24(4):521-36.

COMMENTS ON
"PROPOSED IDENTIFICATION OF ETS AS A TOXIC AIR CONTAMINANT"
Part B, Chapters 1, 3, 4, and 6

FROM: Jennifer Jinot
U.S. Environmental Protection Agency
5 April 2004

Thank you for the opportunity to review your draft Health Effects Assessment for ETS. I apologize for sending these comments late and incomplete (I've only had a chance to review chaps. 1, 3, 4, and 6 so far), but I hope that you might still find them useful.

Chapter 1

1. it's not clear from table 1.2 or from the text in chapter 1 (e.g., 2nd sentence of 3rd paragraph of section 1.0: "Table 1.2 presents estimates of impacts form some of the health effects associated with ETS exposure, and predictions of the numbers of *people* potentially affected in California, ..." [emphasis added]) what the target population of the assessment is. i assume that it is nonsmokers, but active smokers are also affected by ETS. and how are nonsmokers defined? are the population risk estimates for never-smokers only, or do they include long-term former smokers?

2. also in Table 1.2, the attributable risk estimates are presented with too many significant figures. this gives an undue impression of greater precision than there really is.

3. with respect to the actual estimates in Table 1.2, i found the derivations of the OM and SIDS estimates, but i wasn't able to find the derivations of the LBW, PTD, or asthma estimates. if they're not in the assessment, they probably should be, because people are going to be citing the estimates, and some folks will want to know how they were derived.

4. on page 1-10, in the paragraph immediately above Table 1.2, the 3rd sentence doesn't really follow from the 2nd. i think that the intention of the paragraph is to say something more like:

   "With regard to addressing biological plausibility for ETS effects based on active smoking data, analyses based on particular biomarkers should be considered with caution. Presumption of a linear dose-response between an effect and tobacco smoke exposure from either active smoking or ETS exposure as indicated by biomarker measurements ~~and effect~~ can be problematic. The ratios of constituents in mainstream smoke and ETS differs, ..."

5. finally, in the references to chap. 1, there is a Taylor and Tweedie (1997) reference that says it's "in press". surely, that's been published by now if it's ever going to be?

chapter 3

1. it seems that subsections 3.1.2 and 3.1.3, which have to do with ETS *exposure* assessment, should be in their own section rather than part of Section 3.1, which is on mechanisms of injury.

2. at the beginning of Section 3.2.1, it would be helpful to have standard definitions for some of those effects, i.e., LBW, SGA, etc.

3. some of the entries in Table 3.1 aren't consistent in reporting the "n"'s for nonsmokers, but the results presented are for nonsmokers, so it would be helpful to have all the numbers consistently referring to nonsmokers.
   e.g., Ahluwalia et la. n=13,497 for nonsmokers according to the text

4. also some of the "n"'s aren't consistent across the various tables and text in chapter 3. i know that sometimes the original n isn't the same as the n with all the data necessary for analysis, but unless it's explained in the text what the various n's correspond to, the document should consistently use just the most relevant value.
   e.g., for Dejmek et al., Table 3.1 reports n=8,624, but the text (p. 3-30) and Table 3.3 refer to 6,866 mother-infant pairs without any reference to an n of 8624, and of these, 4,309 were reportedly nonsmokers prior to conception. but then Table 3.3 refers to 3710 + 1797 maternal nonsmokers (w/ and w/o ETS), which adds up to 5507, which is close to the 4309 + the smokers who quit in the 1st and 2nd trimester (734 + 467) = 5510. but none of this is clear. and the results presented in Table 3.1 are for the nonsmokers specifically, not for n=8624 or n=6866.

5. in the Jedrychowski & Flak study, i got the impression that the cotinine levels were just used for the validation part of the study. so the results presented in Table 3.1 are for self-reported exposure, right? so i would omit the comment that the cotinine cutoff would mix light and non-smokers, because it makes it appear as if that mixing would be reflected in the reported results, but i don't think that's correct. also, on page 3-15 about the validation part of the study, the cutoff was used to separate smokers and nonsmokers, so the sentence "Nevertheless, based on the 25 ng/mL criterion, the authors found a significant misclassification (false negative) rate of 57% of ETS-exposed women as non-exposed" didn't make sense to me.

6. with respect to the Kukla et al. study, the text (p.3-28) says that babies of mothers passively exposed to > 15 CPD had a mean BW 49 g lighter, but Tables 3.1 and 3.3 say the decrease was 74 g. also there appears to be a typo in Table 3.3 - according to the text and Table 3.1 MNS w/ETS should be 1178 not 1378.

7. in the first sentence of the discussion of Windham et al. (1999) on p. 3-22, i believe that it should read "992 *non*-smokers" not "992 smokers".

8. 2nd-to-last sentence on p. 3-29: i believe that should read "mothers' cotinine levels were

above 1 ng/mL, ..."

9. on p. 3-43, 4th sentence on Chatenoud et al. study: i think that should be: "The OR for SAB associated with ~~parental~~ paternal smoking ..."

10. p. 3-48, 2nd sentence: "But, ..., the risk of a cleft for a fetus of a maternal non-smoker was similar to that of babies who carry the A2 allele and ~~maternal smokers~~ whose mothers were smokers ~~babies carry the A2 allele~~."

chapter 4

1. p. 4-24, section 4.3.2, 2nd sentence: "However ... children persistently exposed to ~~passive smoke~~ ETS ..." [exposure can be passive but not the smoke] similarly, on p. 4-25, 1st sentence of Dollberg et al. discussion, and first line of p. 4-26.

chapter 6

1. the conclusions on asthma induction in children and on asthma induction and exacerbation in adults in this draft are stronger than those in the 2000 National Academy of Sciences report on asthma. i would like to see some discussion of how the current evidence or CalEPA's interpretation of the evidence are different from that 2000 report.

2. i found the discussion of ETS and cystic fibrosis in CalEPA's 1997 ETS report very interesting. i didn't find cystic fibrosis mentioned in this draft at all. is there no new evidence one way or the other on ETS and cystic fibrosis?

3. in Section 6.2.3. it seemed that there were several new studies with strong evidence on lung development in children. i would have expected the updated findings (e.g., Table 6.00) to at least be "Suggestive (strengthened)".

4. in Table 6.01, p. 6-4, re: the Li et al. study. the comments say that "In utero exposure strongly associated with decreased pulmonary function *especially if combined with postnatal ETS* ... [emphasis added]". However, most of the decreases in function listed seem to be of *lower* magnitude for "in utero + postnatal" vs. for "in utero" alone.

5. in Table 6.03, p. 6-15, under the Jindal et al. findings, it should read "1.7 vs. 6.1 $p<0.01$", i.e., the "1.7" is missing.

6. in Table 6.04, p. 6-20, under Li et al. outcome, where it says "overall", the presented OR is for hospitalizations. it appears, though, that it is overall across the age groups since listed below are different age groups, but the age group ORs are for LRIs and the "overall" OR is for hospitalizations.

7. in Table 6.04, p. 6-22, under Peters et al. study description, it says "1.5 - 13 yr-olds"; however, in the text (p. 6-31) it says that the 10,402 children are "ages 8 - 13 years".

8. in Table 6.12, p. 6-49, under Willes et al. exposure, the "15" in "15 ppm" got split across two lines.

9. in Table 6.13, p. 6-57, under Mannino et al. study description, it specifies 4-6 yr olds, and the results are the results for 4-6 y.o.'s, but the N = 13,944 isn't just for the 4-6 y.o.'s, so it could be confusing the way it's presented.

10. in Table 6.13, p. 6-57, under Gergen et al. study description, the "2" is missing from "2 mo. - 5 yr"

11. in Table 6.13, p. 6-59, under Beckett et al. study description, it says "< 19 yr", but in the text (p. 6-67) it says "less than 18 years"

12. p. 6-88, in Table 6.17, under Jaakola et al. study description, it says "18-40 yr old" but in the text on same page its says "aged 15-40".

13. on p. 6-89, the 3rd paragraph begins "*Dubus et al. (1998)*". i think that that should be Abbey et al.

14. on p. 6-90, the 2nd paragraph begins "Emmons et al. (1996)". i think that that one should be Berglund et al. (1999).

March 1, 2004

To: CalEPA

From: Kenneth G. Brown

Re: Comments on "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" A draft report from the California Air Resources Board

I have primarily focused on Section 7.4.1, Breast Cancer. It is obviously difficult to evaluate and compare results from such a wide variety of studies, and you have done a very commendable job.

My comments are in reference to Tables 7.4F and 7.4G, entitled "Summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure" and "Summary risk estimates for ETS and premenopausal breast cancer", respectively. Summarizing the relative risks and confidence intervals by categories of "likely" and "unlikely" missed-important-ETS-exposure is illuminating, suggesting a sensitivity of outcomes to the thoroughness of exposure assessment. Although I think you have used the best single approach, you may be interested in adding results from another approach that is less powerful but is complementary in the sense that it makes different assumptions.

If the studies within a table are independent, and the observed values of RR (odds ratio or relative risk) are equally likely to be too large or too small, then under the null hypothesis RR = 1, the number of observations (S) in which the observed RR exceeds 1 is binomially distributed with parameters N (the number of studies) and P (the probability of an observed value of RR greater than 1). Against the alternative hypothesis that RR > 1 (a breast cancer increase), the null hypothesis is rejected for large values of S. The significance level is the probability that the value of S, or larger, would occur by chance if the null hypothesis is true.

Table	ETS Expos. Missed	N	S	Significance level	
7.4F	likely	10	7	0.17	NS
7.4G	likely	5	5	0.03	S
7.4F	unlikely	5	5	0.03	S
7.4G	unlikely	5	5	0.03	S

Now consider the same approach, except that S is the number of studies in which the lower confidence bound exceeds 1, which means that the null hypothesis (RR = 1) would be rejected for those studies individually against the alternative that RR > 1 with significance level 0.025 or lower (which occurs because the test is one-sided and the confidence intervals are 95%). The assumptions are modified accordingly.

Table	ETS Expos. Missed	N	S	Significance level	
7.4F	likely	10	1	0.22	NS
7.4G	likely	5	1	0.12	NS
7.4F	unlikely	5	5	0.0000	S

7.4G	unlikely	5	5	0.0000 S

The studies for "unlikely" are consistently significant (5 of 5) with rejecting the hypothesis RR = 1 in favor of RR > 1, at the 0.025 level, while the outcomes for the "likely" studies are mixed. It should be noted that the same five studies are "unlikely" in both tables. If these studies are qualitatively better in the sense of having better exposure assessment, they might also be better in other characteristics that could be contributing to the difference in the outcomes.

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Ms Janette Brooks, Chief
Air Quality Measures Branch
CA Air Resources Board
Environmental Tobacco Smoke
1001 I Street
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Sacramento, CA 95812

March 2, 2004

Dear Ms Brooks,

Having commented for the record on OEHHA's 1997 report, "*Health Effects of Exposure to Environmental Tobacco Smoke,*" (Final Draft, February, 1997), I was invited to comment on its current effort, "*Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant,*" (November, 2003.)*

In terms of the current effort, I'll confine myself to reviewing a single troubling facet, *Attributable Risks...* (Table ES.2, p ES-11, Dec. 2003) though it's not the single facet I find troubling in this report.

Let me focus on Low Birth Weight.

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* My comments on the earlier study are scattered throughout its *Appendix B* (June, 1997) as summarized and interpreted (sometimes correctly, sometimes wide of the mark) by the OEHHA staff, without details or verbatims.

LOW BIRTH WEIGHT: THE BODY COUNT

In 1997, based on a number of uncertain assumptions, questionable epidemiology and ballpark statisics (from 1995) OEHHA concluded that: "the proportion of all low birthweight newborns in California that ***may be associated with*** ETS... ***corresponds to*** 1,200 to 2,200 in California in 1995..." and to 9,700 to 18,600 in the nation as a whole (in 1995.)

In 2003, OEHHA now estimates 1,577-1,943 cases of ETS-associated low birth weight in California and 24,253- 29,590 in the nation.

These new national numbers (which have seemingly increased by up to 14,000) are based on a single sub-set, (adult females of all ages) from the NHANES (Pirkle) survey ***of 1995*** (published in '96) which was actually conducted between 1988 and 1991, and which attempted to quantify the exposure of nonsmokers to secondhand smoke (Footnote 1, p. ES-11)

But let's note that a similar survey, NHANES ***1999*** ("*Second National Report on Human Exposure to Environmental Chemi-cals*") showed a 75% decrease in serum cotinine levels in American nonsmokers, indicating (if anything) that exposure to ETS had considerably declined since the earlier report.

I therefore find it disturbing that you'd bypass the later study and choose to employ the former, since using the former stats would over-estimate current exposure.

Then too, and just dealing with the national projections, we ought to consider this. (All stats from the CDC.):

UNITED STATES

Year	total % smokers	% pregnant smokers	% LBW of total births
1985	30.2	NA	6.8
1989	[26.8*]	19.5	7.0
1995	24.7	13.9	7.3
1997	24.7	13.2	7.5
2000	23.3	12.2	7.6
2001	22.8	12.0	7.7
2002	[22.5]**	11.4	7.8

* 1989 estimate based on available figures for 1988 (28.1) and 1990 (25.6)

** Average of available figures for 2002.

In other words, while smoking declined 25% and exposure to others' smoke declined 75%, and the number of pregnant smokers declined 40%+ between 1985 and 2002, low birth rates actually *rose*-- in fact, per the New York Times, to the highest observed levels in the last 30 years. (NY TImes, June 26, 2003)

Further, during the period many other suspected risks (teen pregnancy and alcohol consumption by pregnant women) were also in a decline, while preventive measures increased --with record numbers of women getting early pre-natal care. Logically, at least, this should lead to a clear conclusion that the formerly fingered risks, including smoking and ETS, were not as "causative" as was thought. And that productive investigation should begin on another track.

In light of these easily collected statistics, one wonders why OEHHA relied on a single survey of self-reported exposure for women of all ages ***for 1995*** and factored in none of the later relevant clues.

Questions arise, too, on the California estimates:

Since 1998, California, in isolation, has virtually ended *all* exposure to public smoke and boasts of cutting its rates of smoking by incredibly large amounts (about 5½% below the national average) which would further reduce exposure. Then too, Public Health has so terrified pregnant women on the dangers of ETS, that most women would sooner divorce than let their husbands smoke in the house. Yet the lower range of your estimate has somehow actually climbed (by 377, or 32%) while the upper range has declined by a mere 257. Surely if ETS were a genuine causative factor, your estimate should have declined -- and declined rather drastically-- at both ends of the pole.

So your numbers continue to baffle.

LOW BIRTH WEIGHT: THE EPIDEMIOLOGY

Clearly the RRs from your meta-analysis are factored into your Count.

The most notable thing, however, about *all* the selected studies, both the old and the 7 new, is that what they're all measuring -- each in its own way-- is *lower* birth weight, as importantly distingished from *Low* Birth Weight, officially defined as 5.5 pounds or less.

As OEHHA reported in its first draft revision (6/9/97) the average Lowered Weight among the then-extant studies was

a whopping 28 grams (or just shy of a single ounce.)! (p.20) What are we then to determine are the long-term, or even the short-term, health effects of a difference between a baby born at 6 pounds 7 vs 6 pounds 6? And whatever has this to do with *Low* Birth Weight and all its attendant risks?

Apparently not much. Not even among mothers who actively smoke:

> "The deficits of weight at birth of children born to mothers who smoked during pregnancy are overcome by 6 months of age. "
> – Conter et al, BMJ March 25,1995;320

In 1997, I had commented in detail on the underlying studies (seriously flawed) and OEHHA's conclusions (unwarranted, at best) as they appeared in the "final" February draft. I append those comments. And stand by them still.

Yet OEHHA, based only on the first round of studies (whose results it has now--but only now-- come to admit "*were also consistent with no effect,*" (p 3-36 of the current draft report) had nonetheless, at the time, made a bold statistical leap to RR 1.4 (a number only attained by omitting the negative findings of the largest summarized study) and concluded (on the gamble its assumptions were all correct) that a body count could be had by playing games with the RR. (6/97)

I continue to find it odd that you were willing to count bodies in 1997 based on studies you now admit were con-sistent with no effect but which you'd earlier characterized (p 3-35, Feb. '97) as "provid[ing] sufficient evidence that ETS exposure adversely affects fetal growth."

Point: Which is it? Are a series of flawed studies with weak and, even then, non-significant, results; with a lack of controlled confounders; no grip on misclassification; no trending of dose-response, and, yes, as you mention, "wide

confidence intervals," whose subject, to begin with, wasn't even *Low* weight, but merely a missing ounce-- were they actualy "sufficient" to make a leap to an estimate of vast numbers At Risk? Or-- were they not? And if not (as you now suggest) why on earth did you count bodies on the basis of such dross? And why on earth should we trust you now?

As for the 7 additional studies, they seem to be no better, at least not statistically speaking, and not enough detail is given to say more. ("Other" isn't enough information about confounders. Nor are we told much about the population of mothers.) And though, seemingly, the studies involved actual *Low* Birth Weight, as opposed to a missing ounce (?) one wonders about the studies that OEHHA *didn't* include, and the factors it didn't consider.

For example: After adjusting for active maternal smoking, these are the factors most highly associated with LBW:

Premature delivery:

> "'Ounce for ounce, the babies of smoking mothers had a higher survival rate.' [said Dr. Allen Wilcox, a researcher at the National Institute of Environmental Health Sciences.] Smoking may interfere with weight gain but does not shorten pregnancy. Thus, among smoking women, the smaller babies are more likely to be full term...[I]t's prematurity not birth weight that explains higher mortality.."
>
> -"High Infant Mortality in US Linked to Premature Births," Jane Brody, New York Times, March 1, 1995

Low Socioeconomic Class

> "the most powerful single risk factor."
>
> -Redford et al, JAMA June 3, 1998:279.
> Also Olsen et al, Ugeskr Laeger, Sept 19, 1994:156

Race:

"White infants were heavier and born later than black infants [even though] the white women in this sample smoked more cigarettes"

- Goldenberg et al, Am J Obs & Gyn, Nov., 1996:175

"The rate of Low Birth Weight is twice as high and the rate of Very Low Birth Weight is three times as high for black infants as compared to white infants."

-Luke et al, Int J of Gyn & Obst, March, 1993:40

Poor Nutrition:

"Smoking did not significantly affect infant birth weights." (after adjusting for nutrition.)

-Tchabo, Obst & Gyn, Sept, 1989: 74

"Data suggest that smokers in all social classes have a poorer quality diet."

- Haste et al, Am J Clin. Nutrition, Jan, 1990:51

Occupation:

"A greatly increased risk" for delivering underweight babies was observed among women who worked during their pregnancy. Especially for women required to stand on the job. Job stress, noise and irregular work schedules also increased the risk.

- Am J Obs & Gyn, Sept, 1995.

Other implicated factors:

(Again, after adjusting for active smoking.)Infections. History of induced or spontaneous abortion. First pregnancy after age 30. Medically induced fertilization. Single parenthood. Inadequate weight gain during pregnancy. Chronic illness. Caffeine consumption. Living at a high altitude, and poor dental health.

Surely, not all of these confounders were adjusted for, if indeed such adjustment is actually possible:

> "People...say they'll use statistics to make adjustments for biases and incompleteness. I've spent more than 20 years working as a statistician and I can assure you that you cannot use statistics to adjust."
>
> _Dr. Richard Doll, New York Times, Aug 9, 1994

Then, too, since exposure to smoking has gone down, one might as easily postulate, given the economy, that more women are working (and standing on their feet), or more women are under stress. Or can't afford to go to the dentist. Each of these hypothesis are no less of a reach than fingering ETS, and especially in an era when exposure has declined.

Almost needless to say, I find the rest of your figures in the referenced Table to be equally suspect.

Surely you're aware of the unusual method of reckoning that was used by the EPA to arrive at its estimate of 3,000 lung cancer deaths from ETS. A method that included using recently "former" smokers, assumed that any/ ever exposure was a Risk, and was mainly based on questionable epidemiology on the lifelong spouses of smokers.

Now, climbing on top of that, OEHHA appears to estimate that virtually all lung cancer deaths among non-smokers are caused by ETS!? It hardly pays to ask upon what this is based.

So, too, for the climbing levels of heart disease death you now attribute to ETS. In 1994, the Congressional Research Service called the then-current estimate of 37,000 to be, in a word, "implausible." The escalated Number of 69,000+ is, if anything, doubly implausible.

However, you'll get what you're after from this report, --headlines from an ever-credulous media

I understand the futility of attempting to comment, but conscience compels it.

Sincerely,

Linda Stewart

(LOW BIRTH WEIGHT STUDIES CON'T)

I read (in amazement) the first 35 of these incredibly sloppy studies. (P 3-1 to 3-15). The first thing that hit me was the overwhelming waste--waste of money and waste of time --in the hot pursuit of a fictive grail.

All of these studies had disqualifying flaws. Most predominantly: *no* confounders accounted for. Or *big* ones not accounted for. (Maternal height and weight; or socio-economics; or working status of mothers--an independent risk, see ** below.) And *none* appeared to control for such common-sensical factors as the pregnant woman's diet; or alcohol consumption; or vitamin supplementation....or several other *bigs*. Confounders that were tested for were usually not listed; nor were numbers frequently given. And a number of other factors were *"expected"* or *"assumed"* or *"considered to"* or *"thought to"* but not apparently proved.

Then too we get this: very little or *no* statistical significance and no dose-response (or irrational dose/response), the inclusion of smoking mothers, plus the contradictory data--both between and *within*--all the individual studies.

Then back to semantics. Negative (or seemingly protective) effects are elaborately rationalized and swept under the rug. (eg, *MacArthur and Knox; Ahlborg and Bodin; Zhang and Ratcliffe*) whereas nothing at all's said about the *positive* (or otherwise inculpatory) anomalies in most of the other studies. And the use of deformed children only *may* effect the results?

Your conclusion thus baffles: *"All but one of the studies on the impact of ETS exposure in the home...found a decrement in mean birthweight."* Underwood et al (0.9 for any paternal smoking), MacArthur and Knox (a 100 gram *excess*) Yerulshalmy (1.0 among nonsmoking mothers) Mahtai et al ("no difference in the rates of LBW by mother's ETS exposure).

Is that *one* or is it *four?* And that's *granting* all the stuff that's statistically non-significant (which, as it happens here, is most of the stuff you've got.)

Are you daunted? Uh-UH. You conclude (by projection) from egregiously flawed studies which--if accepted, yield statistical "never-mind"-- that the RR attributable to ETS exposure is "1.2 to 1.4" which you then procede to quantify. Endowing us with images of thousands of scrawny babies left bellowing in their cribs.

This is actually shameful.

- "Comment on OEHHA Assessment of ETS," Stewart, April 28, 1997. From original document.

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March 25, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street
P.O. Box 2815
Sacramento, California 95812

Re: 2003 California Environmental Protection Agency Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"

Dear Ms. Brooks,

Pursuant to your December 17, 2003 invitation for public comment on the 2003 California Environmental Protection Agency Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant," I am enclosing comments prepared on behalf of R.J. Reynolds Tobacco Company. We appreciate the opportunity to participate in this process and expect that our comments will receive appropriate consideration.

Sincerely,

Mary E. Ward

Comments of R.J. Reynolds Tobacco Company ("RJRT") on the 2003 California Environmental Protection Agency Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"

The current California Environmental Protection Agency 2003 Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant," ("2003 Draft Report") does not support designation of environmental tobacco smoke ("ETS") as a toxic air contaminant ("TAC") in California. Additionally, the 2003 Draft Report reaches conclusions regarding ETS and breast cancer that are not supported by the record.[1] Furthermore, new data on ETS and breast cancer published since the 2003 Draft Report must be considered before a final Report is issued.

The 2003 Draft Report Does Not Comply with the Statutory Requirements Pertaining to Designating a Substance as a TAC

The California Environmental Protection Agency's ("Cal/EPA") authority to designate a substance as a TAC is not absolute. Specifically, Sections 39650-39674 of the California Health & Safety Code set forth several requirements that the Agency must meet before designating a substance as a TAC. For example, Section 39660 initially requires Cal/EPA generally to assess the exposure[2] and health effects[3] data for the substance and to specifically determine whether

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[1] Prior to the publication of the California Environmental Protection Agency's ("Cal/EPA" or "Agency") 1997 Report on ETS, RJRT submitted extensive comments to Cal/EPA explaining the basis for RJRT's disagreement with Cal/EPA's conclusions regarding ETS and health. Most of these comments were either rejected or ignored by Cal/EPA. Although RJRT stands by its previously submitted comments, those comments will not be revisited in this letter. Rather, this letter will focus on two issues that are specific to the 2003 Draft Report and thus not addressed in any previous comments by RJRT: 1) the failure of the current Draft Report to meet the requirements set forth in the California Statutes for designation of ETS as a TAC; and 2) the current Draft Report's causal conclusions regarding ETS and breast cancer.

[2] With respect to the ETS exposure assessment contained in the 2003 Draft Report, RJRT has retained Dr. Roger Jenkins to provide comments to Cal/EPA. Dr. Jenkins is a Group Leader and Distinguished R&D Staff Member at

current California ETS exposures are responsible for adverse health effects. If the Agency determines that current California ETS exposures are responsible for adverse health effects, then Section 39660 requires Cal/EPA to provide an estimate of the exposure level that may cause or contribute to adverse health effects in California, *i.e.*, a California-specific risk assessment:

> (2) The evaluation shall also contain an estimate of the levels of exposure that may cause or contribute to adverse health effects. If it can be established that a threshold of adverse health effects exists, the estimate shall include both of the following factors:
>
> (A) The exposure level below which no adverse health effects are anticipated.
>
> (B) An ample margin of safety that accounts for the variable effects that heterogeneous human populations exposed to the substance under evaluation may experience, the uncertainties associated with the applicability of the data to human beings, and the completeness and quality of the information available on potential human exposure to the substance. In cases in which there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposure to the substance.

Cal. Health and Safety Code § 39660(2)

The 2003 Draft Report is completely devoid of any legitimate attempt to comply with these requirements. Assuming *arguendo* that the 2003 Draft Report has reached appropriate conclusions regarding ETS exposures and general health effects, the Report has not "estimated the levels of exposure [in California] that may be responsible for adverse health effects" <u>in California</u>. Moreover, the Report does not express any opinion regarding the existence or non-existence of a threshold level for ETS.

Oak Ridge National Laboratories. He has conducted and published extensive research regarding ETS chemistry and exposures. Dr. Jenkins' comments are based solely on his own expertise in this area and not on any input from RJRT.

[3] With respect to the general health effects conclusions contained in the 2003 Draft Report, RJRT submitted extensive comments to Cal/EPA prior to the Agency's 1997 Report which explained the bases for RJRT's disagreement with these conclusions. Since the stated purpose of the 2003 Draft Report is to propose the listing of ETS as a TAC, RJRT will focus solely on the California-specific requirements set forth in Section 39660 which require the Agency to conduct a California-specific risk assessment for ETS.

Rather than complying with the specific requirements set forth in § 39660(2), the Report employs an overly simplistic and wholly inappropriate approach to attempt to link ETS exposures with specific incidents of disease in California by utilizing the statistical concept of attributable risk.[4] First and foremost, the use of attributable risk calculations requires the underlying epidemiology to be scientifically accurate. For the reasons set forth in RJRT's prior submissions to Cal/EPA, RJRT submits that the underlying epidemiology suffers from substantial scientific inaccuracies which only magnify the inappropriateness of using these studies for attributable risk calculations.

Second, the relative risks used in the attributable risk calculations are not applicable to the California population. The 2003 Draft Report contains no explanation of how the relied-upon epidemiology, even if scientifically accurate, has any relevance to the California-exposed population. The 2003 Draft Report takes great pride in distinguishing California ETS exposures as being substantially lower than the rest of the Country . [See ES-5, 6; IV-8, 9; Table IV-4] Thus, epidemiology studies conducted in other states (and even other countries) would necessarily be premised on populations with higher ETS exposures. Again, assuming *arguendo* that the relative risks from these studies are accurate, these studies provide only limited information about potential risks for the California-exposed population. Thus, using their relative risks for attributable risk calculations in California is wholly inappropriate.

Significantly, for at least three of the diseases that the 2003 Draft Report determined were causally associated with ETS, recent epidemiology studies based solely on California-exposed populations reported no causal association. In a prospective study of 118,094

[4] *See* Attributable Risk Table ES.2 on p. ES-11 and Table 1.2 on p. 1-10.

Californians, Enstrom and Kabat concluded there was no causal association between ETS exposure and lung cancer or coronary heart disease.[5] James Enstrom subsequently petitioned the National Toxicology Program to delist ETS as a "known human carcinogen."[6] Furthermore, in a 2004 study discussed in more detail later in these comments, Peggy Reynolds *et al.*, prospectively followed 116,544 Californians and found no increased risk of breast cancer from ETS exposure.[7]

Additionally, as correctly acknowledged in the 2003 Draft Report, these attributable risk calculations do not address whether there are risks from non-residential and non-workplace exposures in California. Since smoking is banned in practically all indoor environments in California other than in private homes and private automobiles, this omission renders the 2003 Draft Report useless for its stated purpose of determining whether current ETS exposures in California warrant designation of ETS as a TAC and future regulation of ETS in California.[8]

Finally, the flawed use of attributable risk calculations cannot be cured by developing better attributable risk calculations. The simplistic use of attributable risk calculations, regardless of the quality of those calculations, is not appropriate for meeting the requirements set forth in Section 39660(c)(2). While RJRT stands by its belief that ETS exposures in residential

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[5] Enstrom, James E. and Kabat, Geoffrey C., Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98; *BMJ,* 326:1057-66 (2003). The study population was the California subset of the American Cancer Society cancer prevention study (CPS I) that followed 1,078,894 adults from 25 states.

[6] *See* January 14, 2004, letter from James E. Enstrom to C.W. Jameson, Ph.D., of the National Toxicology Program. (Attached as "Exhibit A").

[7] Reynolds, Peggy, *et a.l*, Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, *J. Natl. Cancer Inst.*, 96(1): 29-37 (2004).

[8] Although the Exposure chapters of the 2003 Draft Report spend substantial verbiage attempting to estimate exposure to ETS from sources other than residential and occupational settings, the attributable risk calculations in the 2003 Draft Report make absolutely no effort to characterize any potential risks from ETS exposure in these environments. Therefore, the Report fails to meet this fundamental requirement set forth in the California statutes and does not satisfy the statutory definition of a TAC.

and occupational environments do not cause adverse health effects in adult nonsmokers, that is not the relevant issue for purposes of determining whether the 2003 Draft Report complies with Section 39660(c)(2).

The relevant issue is whether current exposures in California warrant designation of ETS as a TAC and, if so, what are "the levels of exposure that may cause or contribute to adverse health effects [in California]." This issue cannot be evaluated by using attributable risk calculations. The epidemiology studies cited in the 2003 Draft Report do not analyze environments with exposures as low as those currently present in California. Even epidemiology studies that address past exposures in California may not be relevant for this purpose since the need for future regulation cannot be premised on exposure scenarios that no longer exist. Thus, the 2003 Draft Report does not comply with the statutory requirements set forth in Section 39660(c)(2).

The 2003 Draft Report's Conclusions Regarding Active Smoking, ETS and Breast Cancer Are Not Supported by the Record

In 1997, Cal/EPA's Report on ETS examined four studies on ETS and breast cancer and determined there was insignificant evidence of a causal role.[9] Indeed, the 1997 Report did not even conclude that there was "suggestive evidence" of a causal association between ETS and breast cancer.[10] Now, six years later, after reviewing several new epidemiology studies with data remarkably similar to the four studies reviewed in the 1997 Report, the 2003 Draft Report

[9] 1997 Report, p. 7-44. Additionally, in 1997, the Cal/EPA Report referred to the alleged association between "active smoking" and breast cancer as "equivocal."
[10] 1997 Report, p. ES-2.

concludes that ETS exposure is causally associated with breast cancer. This reversal of conclusions is not justified by the record.[11]

First, numerous public health agencies that have investigated the possible relationship between active smoking, ETS and breast cancer and reviewed the same data relied upon by Cal/EPA, have concluded that there is insufficient evidence of a causal role. Cal/EPA is the only one reaching a contrary conclusion.[12]

The International Agency for Research on Cancer ("IARC"), the American Cancer Society ("ACS") and the National Cancer Institute ("NCI") all have evaluated the purported association between active smoking or ETS and breast cancer and concluded that the evidence is insufficient to link either smoking or ETS exposure with breast cancer. For example, in June 2002, IARC issued a press release on secondhand smoke carcinogenicity which stated "[c]oncern that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking [ETS] is unjustified by the evidence."[13] After an extensive literature review on the subject, IARC concluded that the prospective studies "provide no support for a causal

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[11] At RJRT's request, Sanford Barsky, M.D. has submitted his own analysis of the 2003 Draft Report's breast cancer discussion and the literature on ETS and breast cancer. Dr. Barsky is a Professor of Pathology at the UCLA School of Medicine with special interest in breast cancer and lung cancer. Dr. Barsky's comments are based solely on his own expertise in this area and not on any input from RJRT.

[12] Admittedly, RJRT has not always agreed with the conclusions of various public health agencies regarding the association between ETS and disease. In many instances, RJRT's disagreement is premised on the difference between reaching causal conclusions that are based on valid scientific considerations versus those conclusions that are adopted by public health agencies and organizations which appear to be based on the "better safe than sorry" philosophy. While RJRT does not believe that many causal conclusions regarding ETS are supported by the science, we do recognize that public health agencies sometimes have a different standard for reaching causal conclusions to communicate to the public and the media. Therefore, when such agencies have reviewed the data on ETS and a disease such as breast cancer and have publicly stated that the evidence is insufficient to reach causal conclusions, this is particularly compelling and persuasive evidence that the scientific standard for determining causality has not been met.

[13] *See* http://www.iarc.fr/pageroot/PRELEASES/pr141a.html,(Attached as "Exhibit B").

relation" and added that the "lack of a positive dose-response argues against a causal interpretation."[14]

The current ACS website on "What Causes Breast Cancer" does not list ETS among the "lifestyles" risk factors.[15] Furthermore, the ACS does not list active smoking as a risk factor and notes that a link between active smoking and breast cancer has not been found.[16] Likewise, the current NCI website on breast cancer risk factors ("Health Professional Version") does not include ETS or active smoking.[17]

Second, well-respected epidemiologists in the public health community also have agreed that the evidence linking either smoking or ETS with breast cancer is insufficient to establish causality. For example, Jonathan Samet, M.D., senior scientific editor for the 2003 Surgeon General's report on active smoking and the Surgeon General's report on ETS that is currently being drafted,[18] has stated that "investigation of cancer sites other than the lung should be guided by the data from active smokers and by appropriate toxicological evidence."[19] Without scientific consensus that active smoking has a causal association with breast cancer, scientists agree it is biologically implausible that ETS is causally associated with breast cancer.[20]

Contrary to the opinions of every major public health organization and many well-respected epidemiologists who have reviewed the scientific literature on ETS and breast cancer,

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[14] *See* http://www-cie.iarc.fr/htdocs/monographs/vol83/02-involuntary.html, section 5.2. (Attached as "Exhibit C").
[15] http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_breast_cancer_5.asp?sitearea=, Revised 10/02/03. (Attached as "Exhibit D")
[16] Id.
[17] *See* http://www.cancer.gov/cancerinfo/pdq/prevention/breast/healthprofessional/ - Section_175, Revised 2/20/04. (Attached as "Exhibit E")
[18] *See* the Johns Hopkins Bloomberg School of Public Health magazine, http://www.jhsph.edu/Mag_Spring03/smokeout/expert.html. Additionally, on numerous occasions, Dr. Samet has served as an expert witness against the tobacco industry in smoking and health litigation.
[19] Samet, J.M. and Wang, S.S, *Environmental Toxicants: Human Exposures and Their Health Effects,* Chapter 10 - Environmental Tobacco Smoke, (2nd ed. 2000), 319-375, 349. (Attached as "Exhibit F")
[20] Id.

the 2003 Draft Report concludes that the evidence is consistent with a causal association between ETS and breast cancer. However, the Draft contains numerous errors, several misinterpretations and, in many cases, simply fails to explain how it analyzed key studies. First, the bases for the conclusion are wholly unclear, as the Draft does not specify on which data and studies it truly relies. Second, and more important, the data as a whole discussed or cited in the Draft (plus additional data Cal/EPA must consider) does not support a conclusion that a causal association exists between breast cancer and ETS. And finally, because the Draft's conclusion that active smoking causes breast cancer is flawed, it is biologically implausible to conclude that ETS causes breast cancer.

Providing Cal/EPA with meaningful comments on the 2003 Draft Report's section on ETS and breast cancer is difficult because Cal/EPA does not clearly explain on which studies and data it relies. The Draft discusses or cites to approximately 16 new studies on ETS and breast cancer published since the 1997 Report.[21] However, the Draft makes inconsistent references to the studies and inaccurate descriptions of the data. For example, Section 7.4.1.5 states that since its 1997 Report, "[f]our cohort and six case-control studies have reported on breast cancer risk and exposure to ETS."[22] The supporting parenthetical, however, cites a study on <u>active</u> smoking (Terry 2002)[23] and <u>omits</u> one of the cohort studies (Nishino 2001) that examines ETS and breast

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[21] *See* Tables 7.4 E-M, pp. 7-122, 7-137. A precise determination of the number of studies considered in this section of the 2003 Draft Report is difficult since there is inconsistency between studies discussed and those listed in the various Tables. Note, for example, that the Marcus 2000 study is listed in Table 7.4I and two Morabia studies (1998, 2000) are listed in Table 7.4K, but they are not listed in Tables 7.4E or F. The Lui 2000 study is listed in Table 7.4E but not in 7.4F.

[22] Draft Report, p. 7-122.

[23] Terry, 2002. Interestingly, the Terry study observed a risk of breast cancer primarily in women who smoked 40 years or more. Little or no increased risk was observed in women who smoked less than 30 years. (pp. 724, 726). It is biologically implausible that exposure to ETS increases the risk of breast cancer if direct smoking of 30 years or less does not.

cancer risk.[24] Subsequently, in the section titled "Strength and Specificity," the 2003 Draft Report states "three new cohort studies...reviewed for this update did not provide evidence of an association between ETS exposure and breast cancer risk...."[25] Once again, the Nishino cohort study is not included in the parenthetical. Does Cal/EPA rely on three cohort studies or four? Why is the Nishino study not cited with the other cohort studies? Why does the Nishino study receive only cursory discussion later in the section? These Nishino study omissions and the Draft's failure to explain the Nishino study's role in the analysis are especially troubling since Nishino is a statistically significant study showing a protective effect.[26] This type of inconsistency makes it impossible to determine what data Cal/EPA finds convincing enough to conclude a casual relationship exists between ETS and breast cancer.

Furthermore, the "Summary of Risk Estimates" section discusses a review by Kenneth Johnson of 15 published studies and the summary risk estimates reached in this review. However, the Johnson review is "submitted" and is unavailable for independent analysis.[27] Thus, the methodology Johnson used in arriving at these risk estimates is unclear. Nor is it clear how much weight Cal/EPA places on Johnson's review. While the studies included in the Johnson review and the summary risk estimates are listed in Tables 7.4E-G (the first three tables in the

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[24] The Draft Report does briefly discuss the Nishino study later in the ETS section (p. 7-129), but why it fails to cite this study (twice) when listing cohort studies examining ETS and breast cancer risk is unclear. Thus, what weight, if any, Cal/EPA places on the Nishino cohort study in concluding that ETS causes breast cancer is uncertain. Interestingly, Cal/EPA's brief discussion of the Nishino study states, without further analysis, that the relative risk and confidence intervals are as follows: 0.58 relative risk, 95% confidence interval 0.34-0.99. Cal/EPA does not acknowledge that these results show a statistically significant protective effect of ETS on breast cancer. Furthermore, Table 7.4F incorrectly lists the Nishino as a statistically insignificant study with a confidence interval of 0.32-1.1. This type of inaccuracy is troubling and casts doubt on the reliability of Cal/EPA's analysis and conclusions.

[25] Jee 1999, Wartenberg 2000 and Egan 2002 in parenthetical.

[26] RJRT does not contend that the results of this study warrant a conclusion that ETS reduces breast cancer risk. Rather, this study – in combination with all other studies – further demonstrates that Cal/EPA's conclusions regarding ETS and breast cancer are not supported by the scientific literature.

[27] 2003 Draft Report, p. 7-140. A Pubmed search identified no Kenneth Johnson review on ETS or breast cancer published in 2003-04.

Draft listing ETS studies), Tables 7.4H-M contain some studies not included in Tables 7.4E-G (and, thus, apparently not included in Johnson's review). The importance placed on Johnson's review and on all other studies and data must be more clearly explained before RJRT or any member of the public can provide adequate and meaningful comment.[28]

The difficulty in providing meaningful comment regarding Cal/EPA's analysis and methodology is compounded by the fact that the referenced studies provide no basis for Cal/EPA to change the conclusion reached in the Agency's 1997 Report, *i.e.*, that there is insufficient evidence of a causal association between ETS exposure and breast cancer. For example, none of the studies reviewed in the 1997 Report show a relative risk point estimate equal to or below 1.0, but three of the studies since 1997 report relative risks equal to or below 1.0.[29] Of the remaining 13 new studies, more than half are not statistically significant.[30] Thus, if anything, there is less scientific basis in 2003 to conclude that ETS is causally associated with breast cancer.

Cal/EPA tries to explain away the inconsistency between its 2003 breast cancer conclusion and the scientific data by arguing that some studies failed to include childhood or occupational ETS exposure with spousal exposure, resulting in artificially lower relative risk findings.[31] However, Daniel Wartenberg replied to criticism that his study failed to include occupational exposure risks by stating his data showed no increased risk at work, at other

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[28] Because of these concerns regarding the bases for Cal/EPA's conclusions in the 2003 Draft Report, RJRT requests an opportunity to comment again on the revised draft report if Cal/EPA does not change its conclusion that a causal association exists between ETS and breast cancer.

[29] Wartenberg, 2000, Nishino, 2001 and Lash, 2002. Furthermore, Wartenberg and Nishino are prospective studies. The Wartenberg study, funded by the U.S. Environmental Protection Agency among others, followed over 146,000 women prospectively and finds no association between ETS exposure and breast cancer death. The 2001 Nishino study followed 9,675 women prospectively and actually reports a statistically significant reduced risk of breast cancer among women exposed to ETS, as previously discussed.

[30] *See* Tables 7.4F and 7.4I. Interestingly, the percentage of statistically significant vs. statistically insignificant studies is almost identical to the percentage in the 1997 Report, where half of the studies were statistically significant and half were not.

[31] *See* Report, pp. 7-128-30; 7-140; 7-147; Tables 7.4 F, 7.4 E.

locations, or all sources combined.[32] Moreover, the authors of the most recent study that includes childhood exposure in its analysis question the importance of childhood ETS exposure in breast cancer development.[33] Finally, IARC, ACS and NCI considered these same studies and do not differentiate between studies looking at only spousal exposure and those including childhood or occupational exposure. Cal/EPA appears to be making an arbitrary distinction for breast cancer that other scientific organizations looking at ETS and breast cancer risk fail to make.

Finally, the 2003 Draft Report's summary paragraph (p. 7-147) calls into question Cal/EPA's analysis of the data and bases for its conclusion by claiming that "in comparison to studies reviewed in the previous OEHHA report (Cal/EPA 1997), current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk..." (emphasis added). This statement is false. In 1997, four studies were evaluated, all of which had relative risks over 1.0. Two of those four studies had relative risks over 2.0. The 2003 Draft Report evaluated several more studies. Looking at Table 7.4F from the Johnson review, three of the 11 new studies have relative risks of 1.0 or lower, and all three are recent, large prospective studies. Seven of the 11 studies are statistically insignificant. In reality, the 2003 Draft Report shows that the data considered in 1997 was more indicative of an association than the data presented in studies since 1997. The data in the Draft, considered as a whole, is substantially less indicative of a positive association between breast cancer and ETS exposure.

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[32] Draft Report, p. 7-128, citing Wartenberg 2001.

[33] Kropp, p. 522. "Contrary to the assumption that breast tissue is more susceptible to carcinogens at young ages, early passive smoking may not play an important role in breast carcinogenesis."

In addition to its ETS analysis, Cal/EPA also concludes in the 2003 Draft Report that a causal association exists between active smoking and breast cancer. The Draft only addresses direct smoking for biological plausibility, apparently in attempt to bolster an otherwise weak conclusion regarding ETS and breast cancer. Otherwise, this determination has no bearing on ETS as a TAC. RJRT disagrees with the Agency's conclusion that there is a causal association between active smoking and breast cancer.[34]

The 2003 Draft Report's Conclusions Regarding ETS and Breast Cancer Are Not Supported by More Recent Studies on ETS, Breast Cancer and Californians

Additional data published since the release of the 2003 Draft Report further supports the conclusion that there is insufficient evidence that ETS is not causally associated with breast cancer. The Board must consider "all available scientific data" in determining whether a substance is a TAC.[35] On January 7, 2004, a new study was published examining breast cancer risk from active smoking and ETS exposure. *See* Reynolds, Peggy, *et al.*, Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, *J. Natl. Cancer Inst.*; 96(1): 29-37 (2004) ("Reynolds study"). (Attached as "Exhibit G"). Obviously, the Agency staff was unable to consider the Reynolds study in preparing the draft Report since the study was not published until after November 2003. Therefore, the 2004 Reynolds study is not included in the Report. Nonetheless, under California law, it must be considered before a final report is issued for consideration by the Board.

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[34] As discussed in the text above, a conclusion that active smoking is causally related to breast cancer is not consistent with the weight of the scientific evidence. Tables 7.4A&B list studies reviewed on direct smoking and breast cancer. The Tables demonstrate inconsistencies among the studies between the reported risks of breast cancer, and many studies lack statistically significant increased risks.

[35] *See* Cal Health & Safety Code §§ 39650, 39660. The California legislature determined that "the identification and regulation of toxic air contaminants should utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state, and local agencies...." (§ 39650(d)). In evaluating the health effects associated with proposed TACs, "the office shall consider all available scientific data, including, but not limited to, relevant data provided by...academic researchers...." (§ 39660(b)).

The Reynolds study is particularly pertinent to a Californian's risk of developing breast cancer from ETS. The Reynolds study population consists entirely of Californians - a large, prospectively-followed cohort of female professional school employees from the California Teachers Study.[36] Studies have shown that breast cancer incidence varies from one geographic area to another.[37] No other study included in the 2003 Report involves a population of California cancer subjects. Thus, a study population consisting entirely of Californians has significant bearing on the risk Californians face of developing breast cancer from ETS exposure.

The Reynolds study "found no evidence of a relationship between household passive smoking exposure and breast cancer risk."[38] The hazard ratios for developing breast cancer from household ETS exposure were "close to unity for all passive smoking exposure categories examined." The hazard ratios ranged from .87 to 1.01 and were not statistically significant.[39]

The Reynolds study is consistent with the four previous prospective studies that failed to find a statistically significant increased risk of breast cancer from ETS. Therefore, the five large prospective studies conducted since Cal/EPA's 1997 Report reach consistent results, and one study even reports a statistically significant protective effect from ETS. Moreover, these studies, which constitute a substantial portion of the data from the "new studies" reviewed by Cal/EPA since its 1997 Report, do not support an association between breast cancer and ETS exposure.

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[36] "The CTS cohort was established from respondents to a 1995 mailing to all 329,000 active and retired female enrollees in the California State Teachers Retirement System (CalSTRS)." Reynolds, p. 30. 116,544 cohort members were followed from this mailing and 2,005 breast cancer subjects identified. Reynolds, p. 31.

[37] Reynolds, p. 29. Breast cancer is a disease of largely unknown etiology. *See* ACS website, NCI website, *supra* notes 13, 15; Millikan 1998, p. 377. Thus, it is not surprising persons in different geographic areas have different risks of developing breast cancer.

[38] Reynolds, p. 34.

[39] Reynolds, p. 31, Table 2.

In summary, little has changed since 1997, when Cal/EPA correctly concluded that there was insufficient evidence linking ETS exposure and breast cancer. If anything, the additional data published since 1997 provide less support for a causal association between ETS and breast cancer than the pre-1997 data. Therefore, Cal/EPA's strained and novel assertion that a causal association exists between ETS and breast cancer is not supported by the scientific data.

Conclusion

The 2003 Draft Report is insufficient to establish ETS as a Toxic Air Contaminant in California. Cal/EPA has not met the specific requirements for establishing a TAC laid out in Sections 39650-39675 of the California Health & Safety Code. Furthermore, the 2003 Draft Report's conclusion that a causal association exists between ETS and breast cancer is not supported by the current record and is inconsistent with additional scientific evidence not cited in the record.

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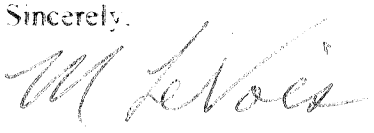
March 25, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attn: Environmental Tobacco Smoke
1001 I Street P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Brooks,

Attached please find my comments on the Draft Report: Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003.

Sincerely,



Maurice E. LeVois, Ph.D.

COMMENTS ON THE DRAFT REPORT:

"PROPOSED IDENTIFICATION OF ENVIRONMENTAL TOBCCO SMOKE AS A TOXIC AIR CONTAMINANT, DECEMBER 2003"

By

Maurice E. LeVois, Ph.D.

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.

Background and qualifications of the author.

I am a consulting epidemiologist with offices in Northern California. I received my B.A. degree from the University of Iowa in 1968, and my Ph.D. degree in health psychology from the University of California, San Francisco, in 1984. I was formerly director of the Veterans Administration's Office of Agent Orange Research and Education, and a scientist in the Agent Orange Study Unit, Centers for Disease Control. Subsequent to my government employment I served for six years as senior scientist at the Institute for Evaluating Health Risks in Washington, D.C. My professional activities have involved the design and conduct of large military cohort studies, occupational mortality studies of PCB exposure, and epidemiologic research on lead exposure in children. I have also designed and conducted large national epidemiological surveys, assessed cancer incidence and reproductive health effects in populations exposed to

agricultural chemicals, studied problems of artifact in epidemiological research methods, and done epidemiologic modeling and failure analysis of toxic waste management facilities. A copy of my *curriculum vitae* is attached.

Over the past decade I have stayed abreast of the published primary epidemiological research reports dealing with environmental tobacco smoke (ETS) exposure and the risk of cancer, coronary heart disease, and various health problems in children. I have published several original research papers, as well as several letters, dealing with various ETS related topics. I have also analyzed many ETS review articles and risk assessments.

I have previously filed detailed comments on draft chapters of the California Environmental Protection Agency's (CAEPA) 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 CAEPA, 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 CAEPA 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.

SECTION I.

Summary of comments that apply to both the 1997 and the 2005 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.

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.

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.

> 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.

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.

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.

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.

> 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.

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.

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.

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 CAEPA 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.

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.

SECTION II.

Sudden Infant Death Syndrome.

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. 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.

Comments on newer studies—

Milerad *et al.* 1998. 1. No control for maternal prenatal smoking in this study; 2. Inconsistent results for cotinine comparisons between SIDS versus accidental deaths (no cotinine difference) and SIDS versus infection deaths; 3. Reduced ETS exposure of infants with infections would be expected -- concerned parents would not be likely to smoke near a sick child.

Rajs *et al.* 1997. Poorly controlled study. Inconsistent results do not support an ETS – SIDS association.

McMartin *et al.* 2002. Inconsistent cotinine and nicotine results indicate unreliable smoking status data. Study can not account for prenatal maternal smoking. Recent ETS exposure may be correlated with cause of death due to recent reduction in exposure of sick infants.

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

Mitchell *et al.* Four papers published by Mitchell and colleagues (Mitchell *et al.* 1991; Mitchell *et al.* 1993; Mitchell *et al.* 1995; Mitchel *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.

The Mitchel *et al.* study design can not separate prenatal and postnatal maternal smoking effects. Mitchel *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). 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."

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.

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.

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." 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."

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.

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

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.

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. 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). As discussed below, the IARC study does not support the Draft Report's conclusion that ETS increases the risk of lung cancer.

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 can not provide anything new.

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.

The Draft Report presents in Part A, Appendix 4 *"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.

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.

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.

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.

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 U.S.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 U.S.EPA risk analysis logic and methods. Even applying the unprecedented 90% confidence interval used in the U.S.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.

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.

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 10.6 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.

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."

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."

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."

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; CL 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)."

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.

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.

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.

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.

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.

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.

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."

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."

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.

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.

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.

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.

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EDITORIAL

The New England Journal of Medicine -- March 25, 1999 -- Vol. 340, No. 12

Passive Smoking, Coronary Heart Disease, and Meta-Analysis

Meta-analysis -- the formal combination of the research results from multiple studies -- is widely used, but with little general understanding of its limitations and uncertainties. There is something quite appealing about collecting all the available research on some question and reducing it to a single figure or a single confidence interval. When properly used, this approach can be useful. However, there is broad evidence that the results of meta-analyses are often not very reliable. LeLorier et al. [1] have shown that many meta-analyses do not agree with the results of subsequent large, randomized trials, and there is little reason to believe that those trials are consistently wrong.

In a review published a few years ago [2], I cited five meta-analyses that produced conclusions that were questionable for a variety of reasons. These included lack of understanding on the part of the meta-analysts of the scientific subject in question or, conversely, lack of understanding on the part of the experts in the scientific subject of the procedure for meta-analysis, failure to consider a host of relevant covariates, and frank bias on the part of the meta-analysis team. Another common problem is lack of homogeneity. When an effect exists, its size may vary substantially from one population to another, such that no combined estimate can have much meaning. (For example, if the rate of some disease is 5 percent among men and 1 percent among women, does it make sense to find that the rate is 3 percent for a person of "average" sex?)

Finally, research studies are not all of high quality, and there is no good way to adjust meta-analyses for variations in quality. Some authors have prepared checklists that can be reduced to a quality score. Studies are commonly weighted according to their quality scores, but the practice is not universal, and even when formal scoring systems are used, poor studies are often weighted too heavily. If some reports are given a quality score of 95 or 100 (of a possible 100), does it make sense for a meta-analysis to include studies scored as 50 and give them 50 percent of the weight given to a nearly perfect study?

Meta-analysis is commonly designed as a series of operations. First, the problem must be stated in terms that can be studied (this sometimes is the hardest step). Second, all the available sources of potentially relevant data must be found and the reports collected. Third, each report is evaluated and an individual summary measure derived (for example, the incidence rate of a disease or an odds ratio). Fourth, the collection of summary measures is interpreted, and a single "best estimate" is derived. Finally, the findings of the meta-analysis are presented. Of these, the fourth step is the most controversial, and because of its limitations, it is sometimes omitted.

In this issue of the Journal, He et al. [3] report a meta-analysis of epidemiologic studies of the relation between coronary heart disease and passive smoking (also known as exposure to environmental tobacco smoke). With regard to this important subject, there is no reliable substitute for epidemiologic research, for several reasons: responses in animals may not be like those in humans, laboratory studies involving human subjects must necessarily be of short duration, and reports of clinical series are subject to a range of serious biases. Can meta-analysis of epidemiologic studies on this topic provide a more reliable conclusion than a thoughtful review of the usual type? There are reasons to think that it cannot.

The first reason is the quality of the data. He et al. [3] found an association between coronary heart disease and environmental tobacco smoke, but most studies of lung cancer and this risk factor have likewise reported a positive association, and those findings have been received with some skepticism because of concern about the quality of the data. Among the reasons for concern are a possible tendency of nonsmokers with lung cancer to look for some external reason (for instance, smoking by a spouse or coworker) for an otherwise inexplicable disease, inaccuracies in the reporting of exposure to environmental tobacco smoke, and reluctance to report a personal history of smoking. He et al. gave little consideration to such possible problems with the quality of the studies they analyzed. Surely not all those studies were perfect.

A second reason for concern is the procedure for meta-analysis itself. The published literature on some topics may reflect the greater likelihood of publication of positive results than of negative results. When study-to-study randomness is considered, the lack of publication of negative studies can sometimes be inferred by analyzing the probability distribution of the results of the studies that have been published. If only the positive part of the probability distribution is represented in the literature, it can be inferred that small negative studies may not have been reported. Ffe et al. [1] examined this matter and obtained a P value that did not indicate statistical significance but that did not exclude the possibility of publication bias. The absence of proof of such bias is not proof of its absence. Analysis of a total of 38 studies, as in this case, can hardly provide much statistical power to detect publication bias.

The authors do not comment on the remarkable uniformity of the findings of the 38 studies, despite the large variations in study design, methods, and populations. For example, if environmental tobacco smoke causes coronary heart disease, why are estimates of this effect from studies that include exposure in the workplace about the same as those from studies that do not? Figure 1 in the report by Ffe et al. shows that study-by-study "best estimates" of the relative risk of coronary heart disease associated with environmental tobacco smoke ranged from slightly over 1.0 to about 2.2. This seems to be a very small range, considering the random variations present in the samples, most of which were small; the large differences in both the methods and the populations examined; the likelihood of confounding, for which there was no adjustment; and the failure to consider the "dosage" of environmental tobacco smoke. A great deal of uniformity among the results of independent studies of a particular phenomenon is not necessarily good; it can suggest consistency in bias rather than consistency in real effects.

Interpretation of Figure 2 in the article is difficult because the reported "linear trend" apparently included analysis of data from persons with zero exposure to environmental tobacco smoke. In view of the potential sources of bias noted above, and in view of the possibility that the never-exposed group had a disproportionally high percentage of persons from population segments generally more careful about health-related behavior (including some religious groups), these data would be more convincing if they showed a significant trend of higher risk with higher degrees of exposure, without including the never-exposed groups.

The authors compared the risk of coronary heart disease in exposed and nonexposed persons in terms of relative risks, but they did not defend their use of that statistical measure or show that it is compatible with their findings. This approach implies a multiplicative model in which risk factors are multiplied rather than, say, added; but why should we expect a complex biologic relation to follow this type of model rather than a model that is linear, or otherwise not multiplicative? In general, mathematical convenience is a common but weak reason for studying relative risks or odds ratios, their surrogates, or any other specific mathematical model.

Perhaps the most troubling aspect of these results is the size of the effect reported. Is an increase in the incidence of coronary heart disease of 25 percent associated with passive smoking compatible with the generally reported increase of about 75 percent among active smokers (a threefold difference)? I find it hard to understand how environmental tobacco smoke, which is far more dilute than actively inhaled smoke, could have an effect that is such a large fraction of the added risk of coronary heart disease among active smokers. Some estimates of the relative risk of lung cancer in association with environmental tobacco smoke are also about 25 percent, but the risk among active smokers is increased by about 1,200 percent over that among nonsmokers. This finding leads to the more plausible conclusion that the added risk of lung cancer that is due to environmental tobacco smoke may be about 2 percent of the risk associated with active smoking.

The clear effects of active smoking on coronary heart disease give us good reason to think that passive smoking might have a similar but much smaller effect. The meta-analysis reported by Ffe et al. [1] meets the accepted technical criteria for meta-analysis, but it suffers from problems inherent in the method, such as deficiencies in the data analyzed. Therefore, I regretfully conclude that we still do not know, with accuracy, how much or even whether exposure to environmental tobacco smoke increases the risk of coronary heart disease.

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Passive Smoking and Coronary Heart Disease

To the Editor:

In their meta-analysis of passive smoking, He et al. (March 25 issue) (1) analyzed 10 cohort and 8 case-control studies and concluded that nonsmokers exposed to environmental tobacco smoke had an overall relative risk of coronary heart disease of 1.25. I want to point out several problems with their analysis. For the cohort studies they analyzed, each adjusted relative risk shown in Figure 1 of their article is higher than the corresponding crude relative risk that can be calculated from the data given in the figure. For example, in the study by Garland et al. (2) the crude relative risk can be calculated as 3.5, and the relative risk reported by He et al. is 4.9, whereas the adjusted relative risk was reported by Glantz and Parmley as 2.7 (3). However, the most dramatic difference occurs in the study by Steenland et al. (4), for which the crude relative risk is 0.54 and the relative risk reported by He et al. is 1.2.

It is often instructive to compare the crude relative risk with the adjusted relative risk to ascertain the influence of the adjustment. With use of the meta-analytic methods of He et al., the overall crude relative risk is 0.84 for the 10 cohort studies. Thus, the conclusion as to whether exposure to passive smoke is harmful or helpful appears to depend on an adjustment process that is often imprecise and ambiguous.

Interpretation of the case-control studies may be even more difficult. Because in a case-control study the relative risk cannot be calculated directly, the odds ratio is used as a surrogate when the disease is rare. However, if the disease is not rare in the particular group being studied (even if it is rare in the general population), then the odds ratio overestimates the actual relative risk. (5) This can yield an exaggerated effect. Furthermore, in a case-control study, what is actually estimated is the relative probability of exposure, given that a person has heart disease. Since heart disease has multiple causes, it is not logical to argue a relative probability (relative risk) of heart disease given that a person is exposed to a particular risk factor. Therefore, the case-control studies should be excluded from the meta-analysis, or at least the cohort and case-control studies should be analyzed separately.

Of course, these considerations would not be relevant if the reported effect of passive smoking were large. It is because the effect is so small that these issues must be taken into account in the final interpretation.

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References

1. He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease -- a meta-analysis of epidemiologic studies. N Engl J Med 1999;340:920-6.

2. Garland C, Barrett-Connor E, Suarez L, Criqui MH, Wingard DL. Effects of passive smoking on ischemic heart disease mortality of nonsmokers. a prospective study. Am J Epidemiol 1985;121:645-50.

3. Glantz SA, Parmley WW. Passive smoking and heart disease. epidemiology, physiology, and biochemistry. Circulation 1991;83:1-12.

4. Steenland K, Thun M, Lally C, Heath C Jr. Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. Circulation 1996;94:622-8.

5. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

To the Editor:

He et al., in their Methods section, erroneously assume that the data presented by Steenland et al. [1] concern American Cancer Society Cancer Prevention studies I and II, when in fact they concern only study II. Because of this error, results from study I were not included in their meta-analysis, a serious omission in view of the large number of cases of heart disease and the lack of relation with passive smoking seen in that study.

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References

1. Steenland K, Thun M, Lally C, Heath C Jr. Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. Circulation 1996;94:622-8.

To the Editor:

I am grateful to these correspondents for raising several issues that need discussion. However, their conclusions are mistaken. In my editorial, I did not deny that there is a relation between passive smoking and coronary heart disease, but I noted that the evidence presented to support a relation is not convincing. It is likely that such a relation exists, but more work will be needed to confirm it, and still more to estimate its strength with much precision.

We must examine evidence that seems to support a favored hypothesis with even more care than we would examine evidence against it. Single-minded dedication to a specific proposition may be useful once other work has clearly shown a need for action, but not before. Furthermore, a well-informed scientist can come up with a plausible explanation for almost any set of research findings. To describe a mechanism by which environmental tobacco smoke might increase coronary artery disease is not to show that it operates in the real world.

Exposure-response relations for toxic agents (excluding many carcinogens) are generally concave upward -- that is, the effects of successively smaller exposures decrease more rapidly than the dose itself, and often something close to a threshold may be found at low doses. The levels of exposure to specific constituents of environmental tobacco smoke are not fully understood, but I do not know of any for which exposures among nonsmokers are as high as one third of those among smokers. This is further reason for caution in concluding that an increase in risk induced by environmental tobacco smoke among nonsmokers is one third or more of the excess risk among smokers.

Other evils of environmental tobacco smoke are well known, and even without coronary artery disease there is strong reason to protect the nonsmoking public. I understand the urge to "pile it on," perhaps in the hope of generating stronger action sooner, and there may be reasons related to public health and public policy for taking action before the evidence is complete. Those reasons are not advanced by overstatement.

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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. 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).

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.

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.

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.

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.

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.

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.

The Draft Report once again repeats inaccurate descriptions of the studies by LeVois and Layard (1995a, and Layard (1995a, 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

Men -- 7758 CHD deaths[4] 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[4] 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[5]

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)

[4] LeVois and Layard (1995)
[5] Layard (1995)
[6] Layard (1995B)

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.

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).

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)

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.

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)[1]

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

[1] 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. Heising, 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.

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. 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	1.13	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*

		Ex-smokers		
	Current smokers	**Years since quit**		
Men		<1 year	1-2	3-5
6-19				
<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.

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.

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.

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.

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.

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.

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).

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.

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=0 40 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.

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 _ and _). 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 (_ _ _). 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 [redacted]."

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 strengthsas a whole, the CPS I cohort is one of the most valuable samples for studying therelation 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. 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 [illegible] and [illegible])."

"Our methodology and results are fully described because of concern that the earlier analysis of coronary heart disease in CPS I [illegible] was flawed by author bias owing to funding by the tobacco industry. Our results for coronary heart disease and lung cancer are consistent with those of most of the other individual studies on environmental tobacco smoke. [illegible] including the results for coronary heart disease and lung cancer in the full CPS I. [illegible] 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, [illegible] 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."

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.

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

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 20-30%. 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:

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.

REFERENCES

(Not cited in the Draft Report)

Bailar, JC. Passive Smoking, Coronary Heart Disease, and Meta-Analysis. Editorial: *NEJM*; Vol. 340, No. 12. 1999

Copas and Shi. Reanalysis of epidemiological evidence on lung cancer and passive smoking. *BMJ*. 12;320(7232):417-8. 2000.

Davey Smith G. Effect of passive smoking on health. Editorial: *BMJ*;326:1048-1049. 2003.

EPA. Risk analysis guidelines. Section: 2.2.1.2. *Criteria for Assessing Adequacy of Epidemiologic Studies*. 1999

Fleiss, J.L. Panel discussion on cardiovascular disease. In: *Environmental Tobacco Smoke Proceedings of the International Symposium* at McGill University 1989. D.C. Heath and Company, Massachusetts/Toronto. 1990.

Forastiere F, Mallone S, Lo Presti E, Baldacci S, Pistelli F, Simoni M, Scalera A, Pedreschi M, Pistelli R, Corbo G, Rapiti E, Agabiti N, Farchi S, Basso S, Chiaffi L, Matteelli G, Di Pede F, Carrozzi L, Viegi G. Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas. *Environ Health Perspect*. 108(12):1171-7. 2000

IARC (V83). *IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Tobacco smoke and involuntary smoking*. Vol. 83. Section 5.1 *Exposure data*. Lyon, France. 2002.

Jenkins RA, Counts RW. Personal exposure to environmental tobacco smoke: salivary cotinine, airborne nicotine, and nonsmoker misclassification. *J Expo Anal Environ Epidemiol*. 9(4):352-63. 1999

Kilpatrick SJ. Misclassification of environmental tobacco smoke exposure: its potential influence on studies of environmental tobacco smoke and lung cancer. *Toxicol Lett*. 1987 Jan;35(1):163-8

Lee PN, Forey VA. Misclassification of smoking habits as a source of bias in the study of environmental tobacco smoke and lung cancer. *Stat Med*.15: 591-605. 1996

Mao Y, Hu J, Ugnat AM, Semenciw R, Fincham S; Canadian Cancer Registries Epidemiology Research Group. **Socioeconomic status and lung cancer risk in Canada.** *Int J Epidemiol.* 30(4):809-17, 2001.

Nilsson R. **Environmental tobacco smoke revisited: the reliability of the data used for risk assessment.** *Risk Anal.* 21(4):737-60, 2001.

Okasha M, McCarron P, Gunnell D, Smith GD. **Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature.** *Breast Cancer Res Treat.* 78(2):223-76, 2003.

Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A. *J Natl Cancer Inst* 7; 96(1): 29-37, 2004.

Trobs M, Renner T, Scherer G, Heller WD, Geiss HC, Wolfram G, Haas GM, Schwandt P. Nutrition, antioxidants, and risk factor profile of nonsmokers, passive smokers and smokers of the Prevention Education Program (PEP) in Nuremberg, Germany. *Prev Med.* 34(6):600-7, 2002.

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EDUCATION

Ph.D. — University of California, San Francisco Medical Center, Graduate Academic Division, 1984.

Dissertation research: Outcome evaluation of the effects of different treatment modalities on the adjustment of children with end stage renal disease.

B.A. — University of Iowa.

EXPERIENCE

1985 to present — LEVOIS & ASSOCIATES
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Consultant in epidemiology and biostatistics. Review and comment on medical and scientific literature for regulatory purposes. Perform meta-analysis and risk analysis--including development of new empirical models for predicting and managing health risks.

1991 to 1997 — INSTITUTE FOR EVALUATING HEALTH RISKS
Washington, DC

Designed and directed epidemiological research projects, including data collection, quality control, statistical analysis, and interpretation.

1984 to 1985 — AMERICAN RED CROSS (ARC), National Headquarters,
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Research consultant to the program planning and evaluation office. Conducted corporate level management and policy research. Reported directly to ARC vice presidents, executive management committee and president. Evaluated a broad range of programs from both policy and operations perspectives.

1983 to 1984 — CENTERS FOR DISEASE CONTROL (CDC)
Atlanta, Georgia.

Agent Orange and Vietnam Experience Studies:
Proposed and demonstrated the feasibility of the Vietnam Experience Study sampling plan. Designed the study questionnaires and survey instruments. Participated in contract development, technical review, proposal selection, and scientific management activities related to the execution of this health study of 30,000 subjects.

Acquired Immune Deficiency Syndrome (AIDS) Activity: Consultant to the CDC AIDS task force and non-governmental scientists involved in studies of AIDS risk factors. Recommended techniques to control the social psychological artifact inherent in AIDS research. Conducted collaborative statistical analyses of AIDS survey data.

1981 to 1983 — VETERANS ADMINISTRATION
Washington, D.C.

Directed the Agent Orange Research and Education Office. Developed a multidisciplinary scientific research and public information program. Coordinated legal and contracting support for scientific and public information projects with combined $12 million budget.

OTHE EXPERIENCE

Spring 1989 — Visiting Lecturer, University of California, San Francisco: Post-doctoral seminars in Health Services Research - use of observational study designs.

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Developed survey methods to establish baseline levels of client satisfaction in compliance with reporting requirements.

SELECTED PUBLICATIONS

Kimbrough RD, Doemland ML, and LeVois ME. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. J Occup Environ Med 41:161-171, 1999.

LeVois ME, Switzer P. Differential exposure misclassification in case-control studies. J Clin Epidemiol Vol.51, No.1, 37-54, 1998.

Kimbrough RD, LeVois ME, Webb, D. Survey of lead exposure around a closed lead smelter. Pediatrics Vol.95, No.4: 550-554, 1995.

Kimbrough RD, LeVois ME. Management of children with slightly elevated blood lead levels. Pediatrics Vol.93, No.2: 188-191, 1994.

Zhai S, Kimbrough RD, Bo Meng JH, LeVois ME, Xiang H, Xuenian Y. Kashin-Beck Disease: A Cross-sectional Study of Seven Villages in the Peoples Republic of China. Journal of Toxicology and Environmental Health Vol.30: 239-259, 1990.

Carlo GL, LeVois ME, Godfrey LR. Public health claims under Superfund, new data and tools for estimating liability and apportioning claims. Environmental Claims Journal Vol.1: No.2, 1989.

Carlo GL, LeVois ME, Lang BE. The Public Health Authorities of Superfund: New Areas of Significant cost Liability. Chapter in: Insurance Claims for Environmental Damages: Legal and Technical Considerations. EEPC Publishers, New York, 1988.

LeVois ME, Nguyen T, Attkisson C. Artifact in Client Satisfaction Assessment: Experience in Community Mental Health Settings. Evaluation and Program Planning Vol.4 pp. 139-150, 1981.

Published Abstracts

LeVois ME, Carlo GL. Diagnostic Suspicion Bias: Reye's Syndrome and Aspirin. Abstract published in American Journal of Epidemiology Vol.128: No.4, pp.939, 1988.

Carlo GL, Doemland ML, LeVois ME, Ponomarenko T. Expanding the Interface Between Epidemiology and the Law: A Model for Settlement of Toxic Torts. American Journal of Epidemiology Vol.124: No.3, September 1986.

Invited Papers

LeVois ME. Granite City, Illinois, lead exposure study. Paper presented at the Annual Meetings, Society for Risk Analysis, Baltimore, Maryland, December 6, 1994.

LeVois ME, Carlo GL. Diagnostic Suspicion Bias: Reye's Syndrome and Aspirin. Paper presented at the Annual Meetings, Society for Epidemiologic Research, Vancouver British Columbia, Canada, June, 1988.

LeVois ME. Artifact in Epidemiological Research: Reye's Syndrome and Aspirin. Invited paper presented to Roswell Park Memorial Instute, Division of Social and Preventive Medicine, Seminars on Current Issues in Epidemiology, Spring, 1988.

REFERENCES AVAILABLE UPON REQUEST

Michael J. Thun, MD, MS
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March 11, 2004

Janette Brooks, Chief
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Dear Ms. Brooks:

Enclosed, please find the comments of epidemiologists at the American Cancer Society regarding the Draft Report, *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003*. None of our staff will be available on March 15 to participate in the meeting about this report. We hope that the written comments will be helpful to the Air Resources Board in revising this important document. Please feel free to contact me by telephone (404-329-5747) or email (mthun@cancer.org) regarding questions or clarifications.

Sincerely,

Michael J. Thun, MD, MS

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Comments on California EPA draft Health Effects Assessment for ETS

Michael J. Thun, M.D. (Draft March 12, 2004)
American Cancer Society, Atlanta, GA.

The California Environmental Protection Agency (Cal/EPA) is to be commended for its comprehensive review of the scientific literature on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (*1*). This update of a previous Cal/EPA monograph (*2*) adds valuable information on the extensive clinical and experimental evidence regarding ETS and heart disease from studies published since 1997. It is notable that the previous Cal/EPA report was the first to draw widespread attention to the adverse cardiovascular effects of ETS exposure. This relationship is now well established, due in part to the groundbreaking contributions of Cal/EPA.

The current draft report concludes that ETS exposure is causally related to cancers of the lung, breast, and nasal sinuses (Page 7-1). The relationship between ETS and breast cancer is said to appear stronger for pre- than post-menopausal breast cancer. In this report, Cal/EPA again distinguishes itself by providing an update of the evidence on ETS and lung cancer, and by drawing attention to the accumulating evidence concerning breast cancer and second hand smoke. However, the conclusions of this report with respect to breast cancer conflict with that of a working group of the International Agency for Research on Cancer (IARC) (*3*). IARC characterized the evidence regarding ETS and breast cancer as "inconsistent". The conclusions of Cal/EPA and IARC also differ with respect to cancers of the nasal cavity and paranasal sinuses. Both the current and previous Cal/EPA report include cancer of the nasal cavity as causally related to ETS. IARC lists cancers of the nasal cavity and paranasal sinuses among the 15 cancer sites caused by active smoking, but does not designate either of these cancers as causally related to ETS.

The question of whether ETS, or more generally tobacco smoke, causes breast cancer is extremely important. If passive smoking does cause breast cancer, then policies that reduce ETS exposure will help to prevent this cancer and will strengthen the social mandate to protect non-smokers from second-hand smoke. However, if the evidence is not conclusive at this time, then a premature decision about causality could jeopardize the credibility of the entire review process. The current evidence that ETS exposure causes lung cancer and heart disease is convincing. It is crucial that other conditions be added to this list only if the evidence supporting a causal relationship can withstand careful scientific scrutiny.

Epidemiologists at the American Cancer Society (ACS) (Thun, Henley, Oltmanns, and Calle) have carefully reviewed the sections of the report pertaining to breast and nasal sinus cancers. We evaluated this evidence in relation to the Cal/EPA criterion that "chance, bias, and confounding can be ruled out with reasonable confidence" (page 1-9). At present, we do not believe that the published evidence meets these criteria for cancers of the breast or nasal sinuses, although we do believe that breast cancer in particular is an important topic for continuing research. We offer the following comments for consideration.

General Comments

1) The summary of the epidemiologic evidence concerning breast cancer (pages 7-132 to 7-147) offers four hypotheses, listed below, to explain why published studies of active smoking and/or ETS exposure have not consistently found increased risk of breast cancer risk in exposed women. However, the discussion of this evidence, in terms of its consistency, strength and specificity, and limitations, is relatively brief. This section needs to be expanded and broadened to assess systematically the extent to which published studies support or conflict with the hypotheses proposed. It also needs to consider other potential limitations of case control studies, particularly biases that may be introduced by the use of highly selected reference groups.

2) The hypotheses proposed to explain the lack of association between breast cancer and active and/or passive smoking can be paraphrased as follows (page 7-133):

    a. The dose-response relationship between exposure to tobacco smoke and breast cancer risk may be non-linear. According to this theory, low doses of tobacco smoke (such as result from ETS exposure), may increase risk, whereas higher doses (such as those due to active smoking) may obscure this risk, because of the antiestrogenic effects of active smoking. This theory is proposed to explain why ETS may increase breast cancer risk, even though active smoking does not.

    b. Tobacco smoke may increase breast cancer risk only in a genetically susceptible subgroup of women. This theory suggests that studies that combine all women and do not stratify on genetic susceptibility may obscure an association.

    c. Human breast tissue may be vulnerable to exposure to tobacco smoke only during certain critical time periods. For example, vulnerability may be greatest between menarche and first pregnancy, as is the case with ionizing radiation. Epidemiologic studies that define ETS exposure in other ways (such as years of childhood exposure, cumulative exposure, or continuing exposure) may misclassify the biologically relevant exposure and thus fail to detect a real association.

    d. Tobacco smoke may affect certain types of breast cancer but not others. For example, some studies have reported increased risk only in relation to premenopausal breast cancer.

3) Any or all of the above hypotheses are biologically plausible. However, the hypotheses themselves do not constitute evidence that active or passive smoking causes breast cancer. Additional evidence supporting these hypotheses is particularly necessary because of the large published literature that shows no

overall relationship between active smoking and breast cancer. As noted by IARC; "..the lack of an association with active smoking weighs heavily against the possibility that involuntary smoking increases the risk of breast cancer, as no data are available to establish that different mechanisms of action are in play at the dose levels of active and involuntary smoking." In revising the report, Cal/EPA should systematically examine which studies (basic, epidemiologic and other) support each hypothesis and which do not. The following points, in particular, need attention.

a. The report should acknowledge that extensive epidemiologic data shows no overall association between active cigarette smoking and incident breast cancer, in analysis that include women exposed to ETS in the referent group. A meta-analysis of 53 epidemiological studies found that, among 22,255 women and 40,832 controls who drank no alcohol, there was no overall association between active cigarette smoking and breast cancer [RR=0.99 (95% CI=0.92-1.05)] (Figures 1 & 2) (*4*). All of the studies in this analysis had individual information on reproductive risk factors for breast cancer and hormonal therapies with which to control for these factors. Alcohol consumption was unequivocally associated with breast cancer in these studies and correlates strongly with active smoking (and possibly with ETS exposure). Therefore, it is essential that studies of active or passive smoking in relation to breast cancer be able to control for alcohol consumption, which some have not.

b. At least six studies of active smoking and breast cancer have examined the association with and without exclusion of ETS exposed women from the referent group (Figure 3). Four of these studies show some increase in the relative risk (RR) estimate when ETS women are excluded (Morabia 1996, Johnson 2000, Kropp 2002, Egan 2002) while two show either no increase (Marcus 2000) or a decrease (Reynolds 2004). In no study is the effect of this exclusion statistically significant. The increase in the relative risk estimate resulting from the exclusion appears to be larger and more consistent in the case control studies than in cohort analyses, raising concerns about potentially biased reporting of exposure in retrospective studies. At least five case control studies featured in the Cal/EPA report (Sandler 1985, Morabia 1996, Lash 1999, Johnson 2000, Kropp 2002) and one prospective study (Reynolds 2004) found an association between active smoking and breast cancer incidence, even when they did not exclude ETS exposed women in the referent group. The observed association is so strong in two studies (Sandler 1985 & Morabia 1996), that if it were real, some increase in risk would be apparent in most studies of active smoking, irrespective of methodological differences. Cal/EPA needs to address the potential for biased reporting of exposure in case-control studies in the section on "Limitations of studies (7-139 to 7-140), and possibly in the summary on page 7-147.

c. Perhaps the most critical factor not considered by the Cal/EPA report is the potential for bias in studies that exclude women with any exposure to passive smoking from the referent group. This is particularly problematic in case control studies where women recall their ETS exposure retrospectively, already knowing whether they have breast cancer. Most women in Western countries who are old enough to develop breast cancer have had substantial past exposure to ETS. The subgroup of women designated as never-active, never passive smokers comprises a small percentage of all never-smoking women (about 10% in the study by Johnson et al., 2000). Reliance on a small and highly selected referent group may introduce serious problems with both the validity and statistical precision of these studies. In general, the published studies do not provide information about the demographic and behavioral characteristics of women in the referent group who report neither active nor passive smoke exposure. Reliance on a highly selected control group may introduce more biases than it removes.

d. In summarizing the epidemiological evidence (pages 7-132 to 7-139), Cal/EPA should acknowledge that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure. These studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer. In at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. The prospective data should be considered far more seriously in weighing the totality of the evidence than has been the case in the current draft.

e. The Cal/EPA report cites at least ten studies that have evaluated the association of breast cancer with active or passive smoking in relation to specific genetic polymorphisms (Ambrosone 1996, Millikan 1998, Morabia 2000, Chang-Claude 2002, Zheng 1999, Gammon 1999, Conway 2002, Brunet 1998, Ishibe 1998, Zheng 2002). All of these studies have limited statistical power to assess gene-environment interactions, and report conflicting findings (Figures 4a-4d). For example, Ambrosone 1996 found increased risk of post-menopausal breast cancer associated with active smoking only among women with slow acetylator NAT2 genotype. This conflicts with the findings of Morabia 1998, that showed increased risk in both slow and rapid acetylators and with the results of Millikan 1998, who found no association for either genotype. Even more limited are studies regarding polymorphisms in NAT1 (Zheng 1999), p53 (Gammon 1999), or BRCA1 and BRCA2 (Brunet 1998). While it is legitimate to hypothesize that genetic susceptibility may modify the relationship between tobacco smoke and breast cancer (pgs 7-132 & 7-

133), the hypothesis is not currently supported by studies of this issue. The inclusion of Figure 7.4.3 (page 7-138) suggests that that the results currently available on genetic susceptibility provide reasonable support for a causal relationship between ETS and breast cancer. Since this is not the case, we suggest that Figure 7.4.3 be dropped unless it is used to illustrate the inconclusiveness of currently available data.

f. Studies of the timing of tobacco smoke exposure in relation to breast cancer risk are similarly inconsistent (Figure 5). Two studies (Morabia 1996 & Lash 1999) report an equivalent increase in risk associated with active smoking whether smoking began before or after the first pregnancy; Band 2002 reports an association with premenopausal breast cancer only when active smoking occurs before the first pregnancy; Kropp 2002 and Egan 2002 report no significant difference related to the timing of exposure. Reynolds 2004 reports some increase in the risk of post-menopausal breast cancer in women who smoked at least five years before first pregnancy.

g. The data in figures 2-4 are equally inconsistent with regard to risk of pre- versus post-menopausal breast cancer in studies of active smoking or ETS exposure. The currently available data do not convincingly demonstrate a stronger association of ETS with any particular type of breast cancer, nor do they establish that past studies underestimated the association by studying the wrong endpoint.

Specific comments:

1) Page 7-79 through 7-81: It is important not to confuse studies of nasopharyngeal cancer with those pertaining to nasal sinus cancer. Both are extremely rare in the United States, but nasopharyngeal cancer is not rare in certain Asian and native-Alaskan populations. The only studies cited that pertain to nasal sinus cancers were those reviewed in the 1997 Cal/EPA report. All of the newer studies pertain to nasopharyngeal cancer. IARC reviewed the studies of active and passive smoking in relation to cancers of the nasopharynx, nasal cavity, and paranasal sinuses. IARC concluded that active smoking was causally related to cancers of the nasal cavity and paranasal sinuses, but that the evidence regarding ETS exposure was "conflicting and sparse". It was considered implausible that the association seen with ETS in these studies was stronger than that seen with active smoking.

2) Page 7-92, Active Smoking, line 6: The Wartenberg et al. 2000 study considered only second-hand smoke and should not be listed here. The correct reference is Calle et al., 1994 (*5*), who studied active smoking in relation to fatal breast cancer in the ACS cohort. The study by Terry et al. 2002 should be cited here rather than on page 7-122 (2nd last line) because it concerns active smoking.

3) Page 7-134, 2nd full pp, 1st sentence: While it is true that there is concordance between animal and human susceptibility to carcinogenesis from a particular exposure, there is much less concordance with the affected site.

4) Page 7-134, last pp: The report should acknowledge that animal models of mammary cancer are less predictive of human breast cancer than are animal models of certain other cancer sites.

5) Page 7-136, 1st pp, 1st sentence: While the sentence is technically true, three of the studies cited (Santella 2000, Rundle 2000, and Li 2002) mention finding no association between smoking status and the formation of DNA adducts or oncogene formation in breast tissue.

6) Page 7-136, 1st pp, last sentence: Whyatt et al. 1998a measured DNA adducts in placental tissue; Anderson et al. 2001 measured urinary excretion of nicotine metabolites. These studies do not directly involve breast tissue.

7) Page 7-136, 2st pp: None of the studies cited above document DNA adducts or mutations in breast tissue due to ETS.

8) Page 7-137, Figure 7.4.2: The horizontal dotted line should represent a RR of 1.0 on the Y axis, not be below it. If this line is repositioned the results by Lash 2002 will be below the line. The selection of studies included in this graph is puzzling. The subgroup findings from Johnson for women > 35 years should not be included, whereas the results from Morabia 1996, Chang-Claude 2002, Egan 2002, and Reynolds 2004 should be added.

9) Page 7-138, top pp: The issue of the "consistency" of results from the case-control studies only becomes important if one has satisfied considerations of validity.

10) Page 7-13, top pp & Figure 7.4.3: See general comment 3c above.

11) Page 7-144, Figure 7.4.4: The scale on the Y axis should consistently be either arithmetic or log transformed but not both. Use of the log transformed scale may obscure the degree of variability across studies and the implausibly large RR estimates in some studies. Hirayama 1984 or Sandler 1985 should presumably not be included in the Figure, since their published analyses were incomplete and did not control for the established risk factors for breast cancer.

12) Page 7-146, Figure 7.4.5: Several studies included in this figure do not control for important covariates such as age at first birth and/or alcohol consumption (Hirayama 1984, Sandler 1985, Smith 1994, Millikan 1998, Delfino 2000).

References

(*1*) California Environmental Protection Agency. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Part B: Health Effects. Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assesment; 2003.

(*2*) California Environmental Protection Agency. Health Effects of Exposure to Environmental Tobacco Smoke: Final Report. Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assesment; 1997.

(*3*) IARC. Tobacco Smoke and Involuntary Smoking. Vol 83. http://193.52.164.11/htdocs/monographs/vol83/02-involuntary.html ed. Lyon: International Agency for Research on Cancer; 2004.

(*4*) Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. British J Cancer 2002;87:1234-45.

(*5*) Calle E, Miracle-McMahill H, Thun M, Heath CJ. Cigarette smoking and risk of fatal breast cancer. Am J Epidemiol 1994;139:1001-7.

Figure 1: Studies of Breast Cancer & Active Smoking

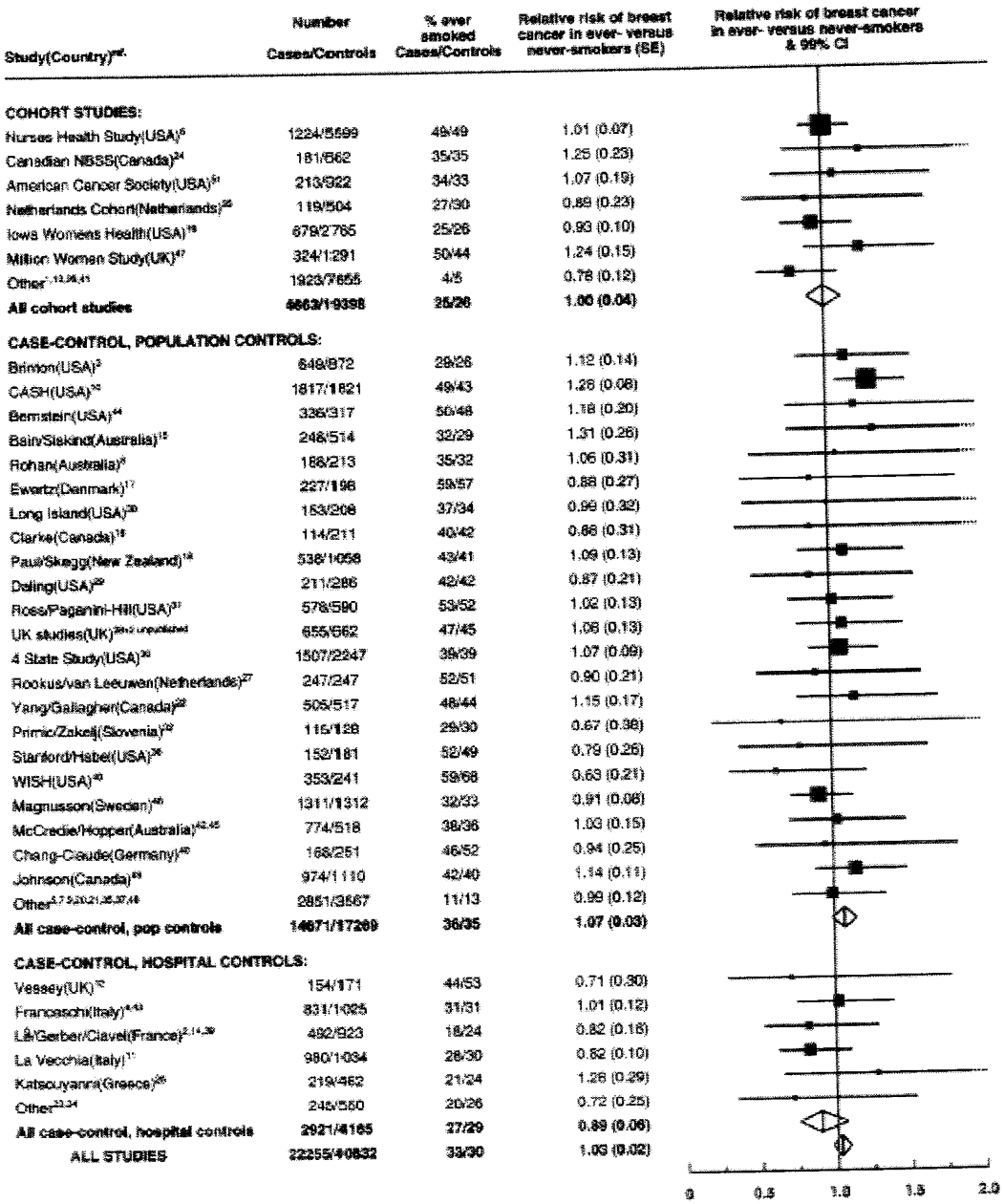


Figure 2:Breast cancer & ever smoking by subgroup

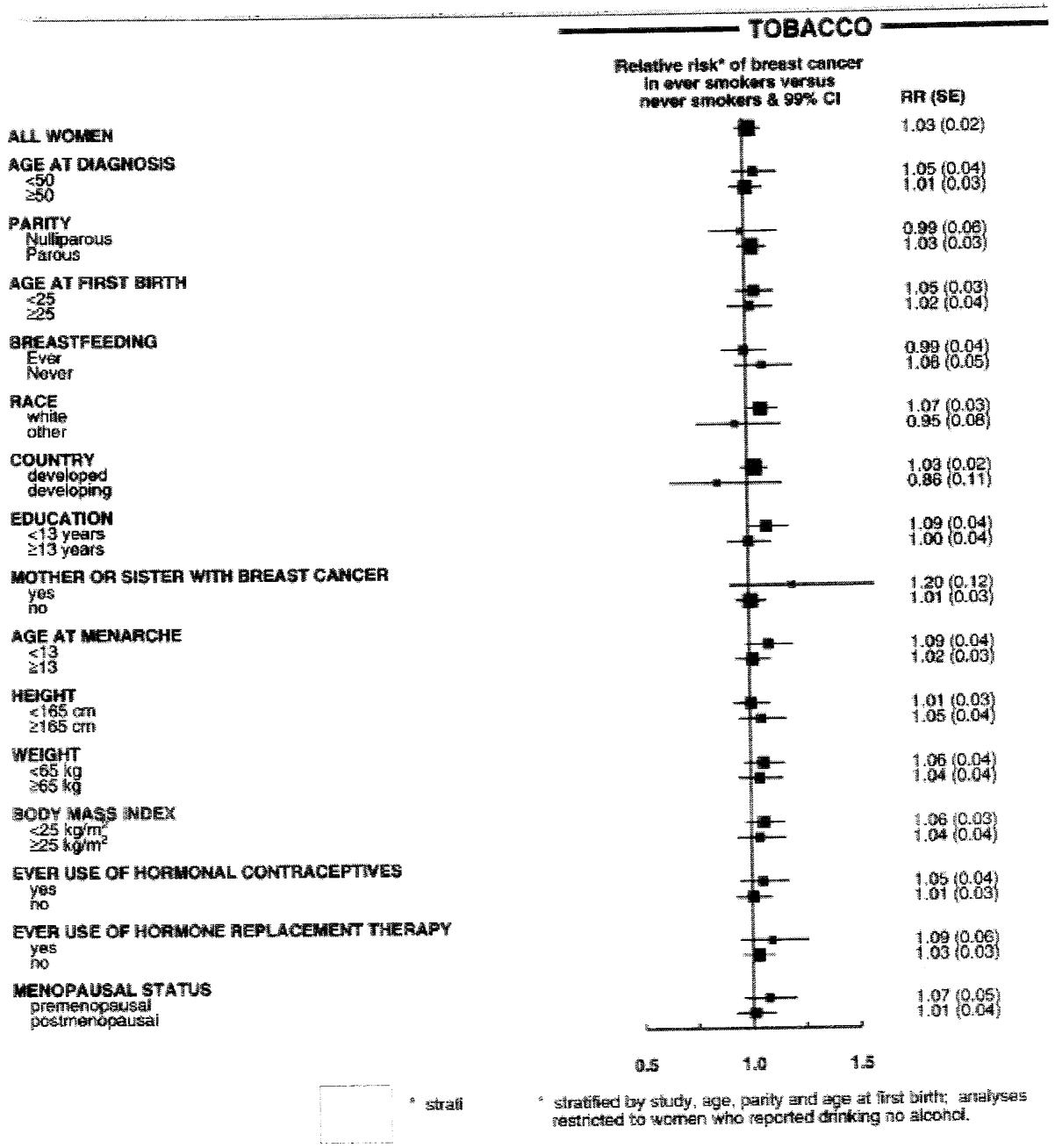


Figure 3. RR for Breast Cancer Among Current Active Smokers When Referent Group Includes (+) or Excludes (-) ETS Exposed Women

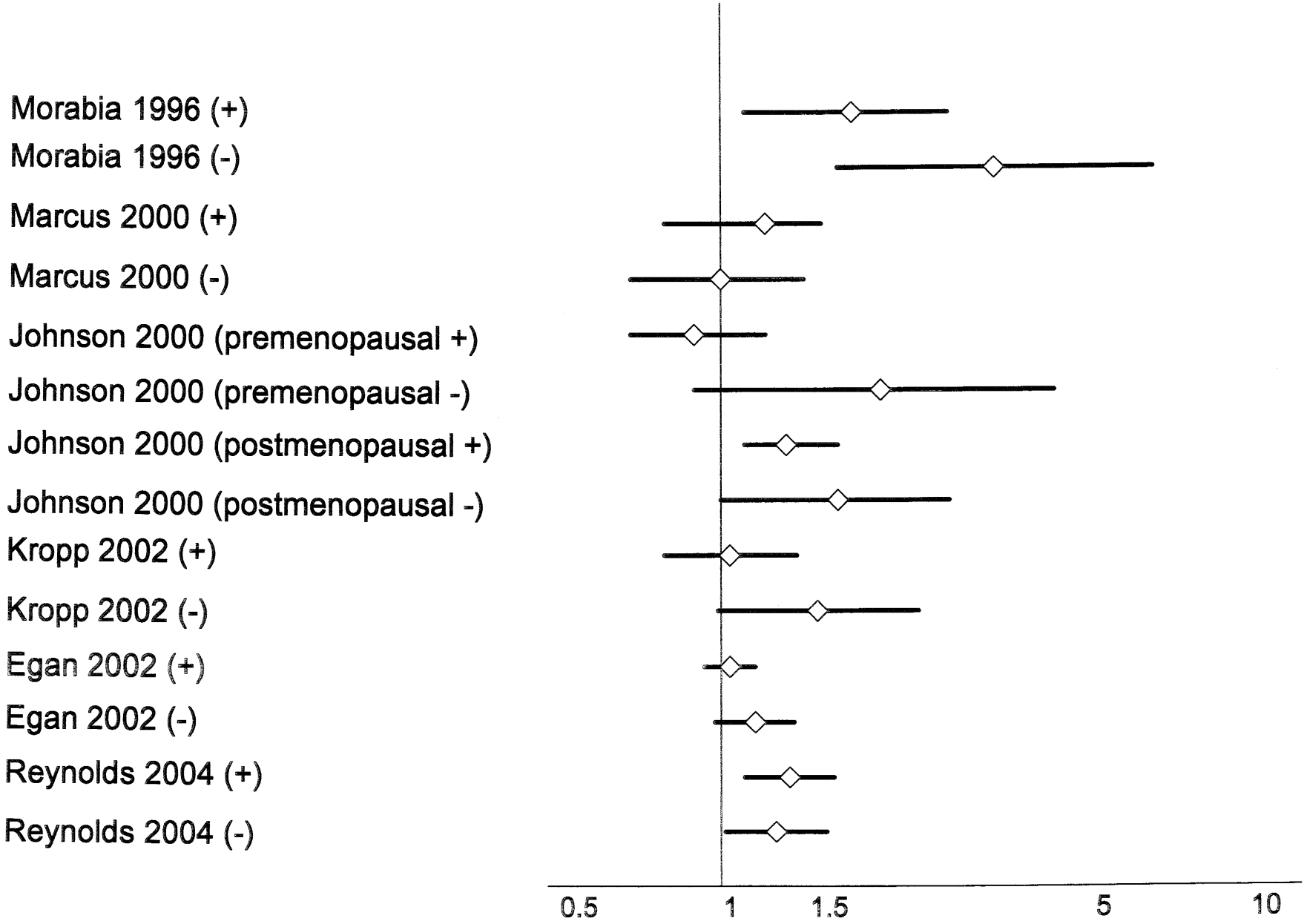


Figure 4a. NAT2 Susceptibility to Develop Breast Cancer from Current Active Smoking

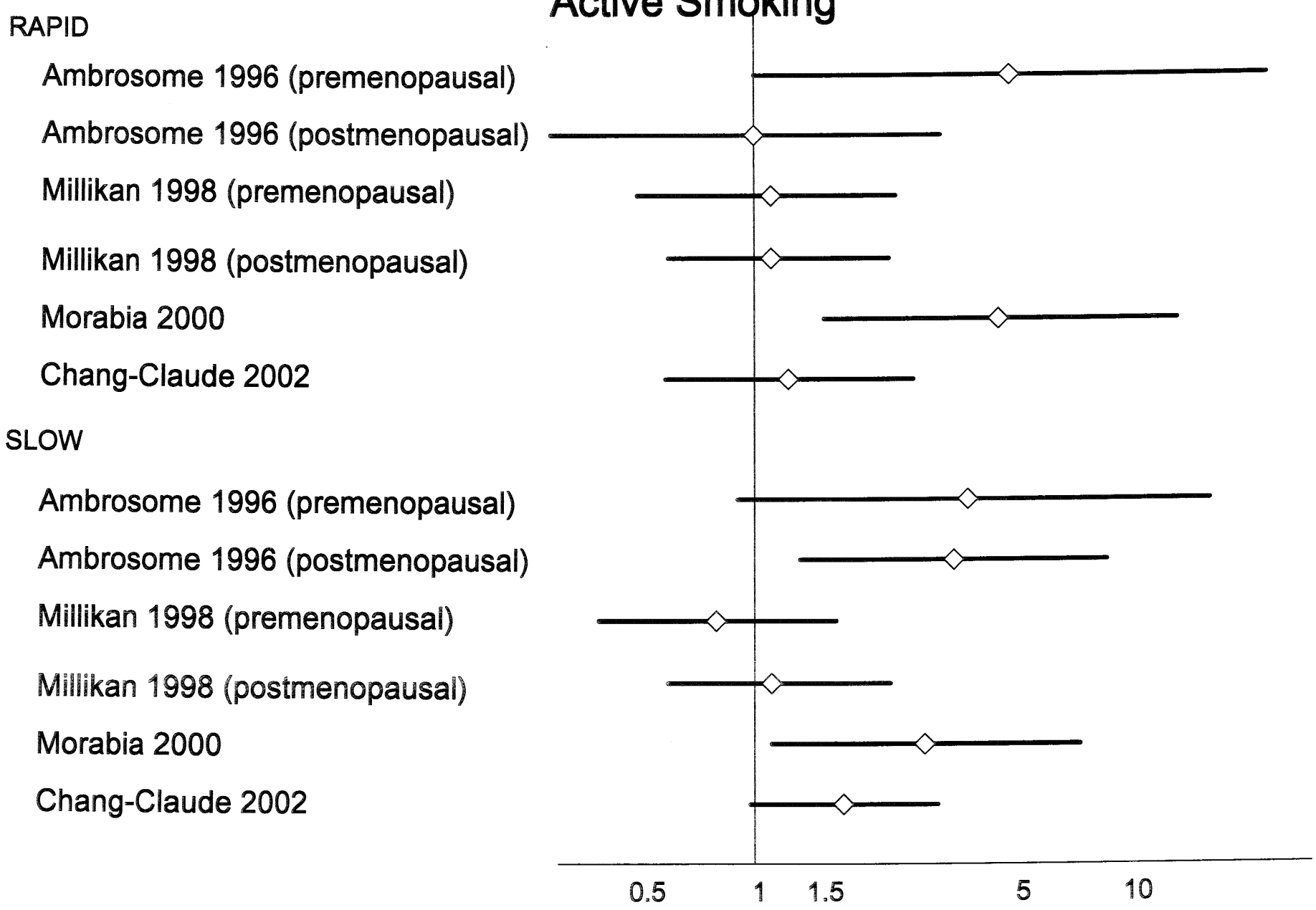
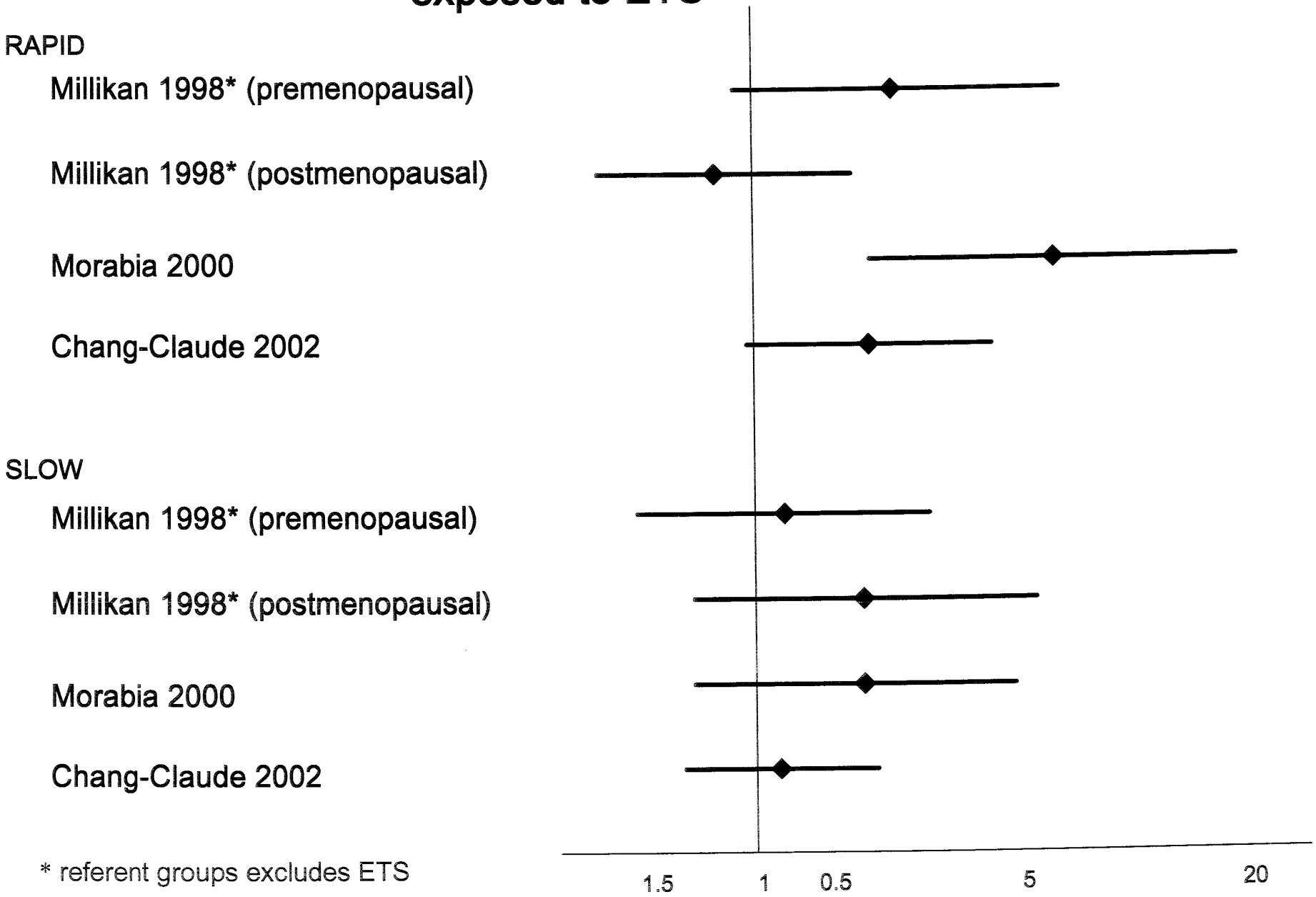


Figure 4b. NAT2 Susceptibility to Breast Cancer for Women ever exposed to ETS



* referent groups excludes ETS

Figure 4c. Genetic Subgroup Susceptibility to Breast Cancer from Current Active Smoking

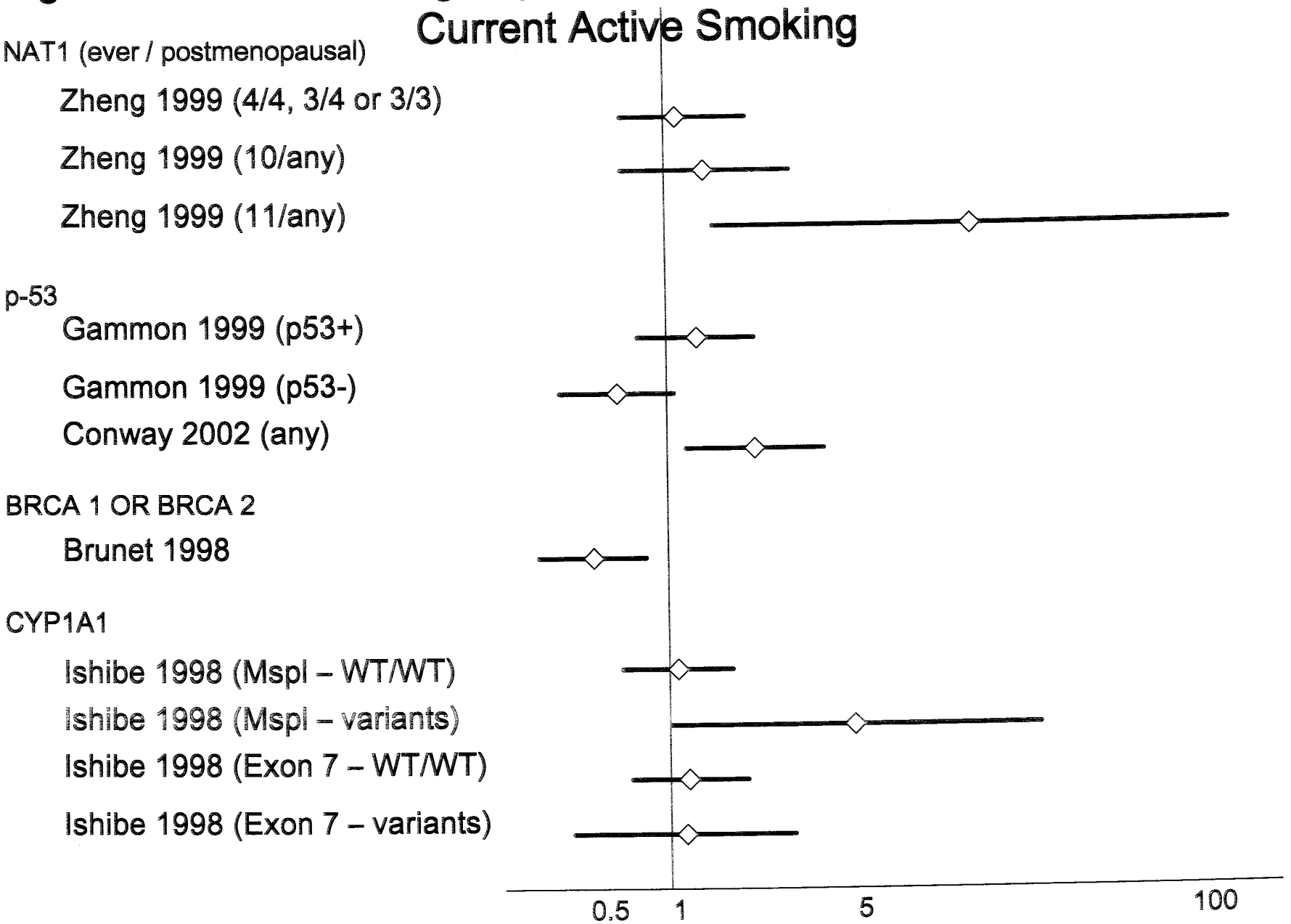


Figure 4d. Genetic Susceptibility to Breast Cancer from Current Active Smoking

Zheng 2002

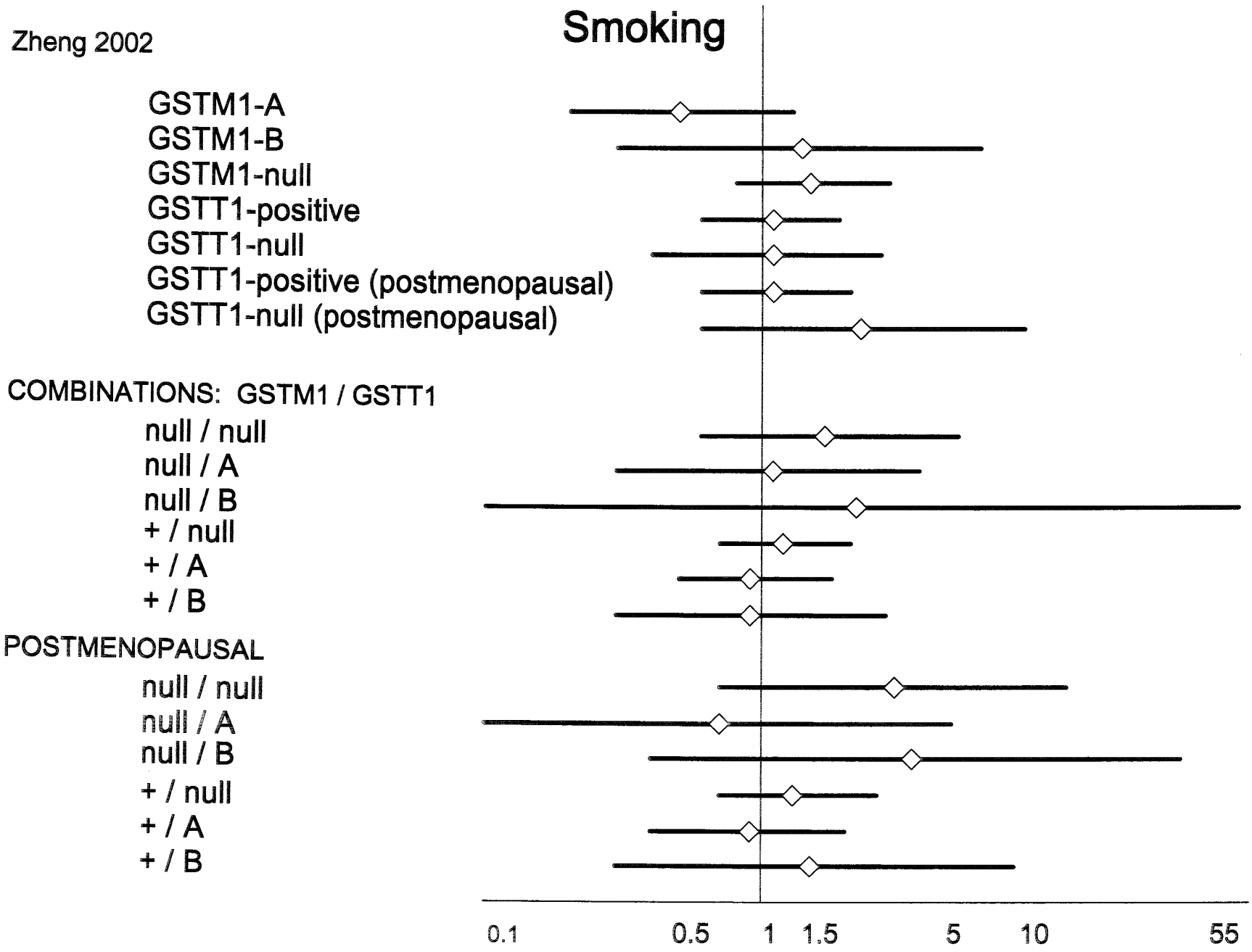
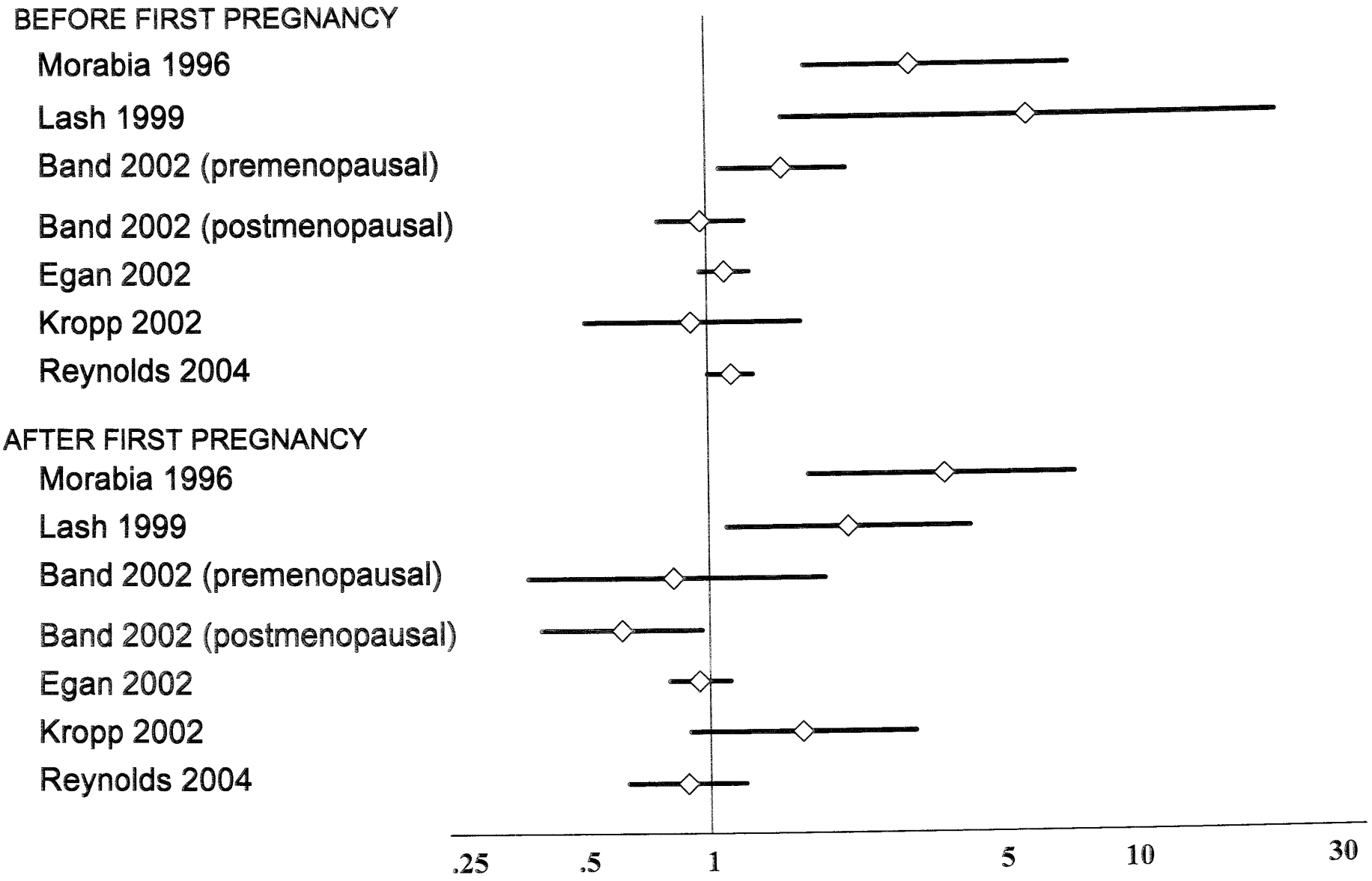


Figure 5. Timing of smoking and breast cancer risk



Comments on California EPA draft Health Effects Assessment for ETS

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I have reviewed the March, 2005 draft of the California Environmental Protection Agency (Cal/EPA) evaluation of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (*1*). The Agency is to be commended for revising the draft extensively in response to public comments. At this point I still consider the evidence that tobacco smoke increases breast cancer risk to be limited rather than sufficient, according to the IARC criteria. This is not the same as rejecting the possibility that ETS and/or active smoking may affect breast cancer risk. It means only that the currently available evidence for this is limited.

I am concerned that, despite the revisions, this draft of the report still describes the evidence concerning breast cancer in a manner that overstates its strengths and minimizes its limitations. This weakens rather than strengthens the effectiveness of the report in my view. At present, the conventional wisdom among breast cancer researchers is that tobacco smoke (either as active smoking or as ETS exposure) has not been shown to affect breast cancer risk. If OEHHA wishes to change this, it must discuss the available evidence accurately and objectively, acknowledging both its strengths and limitations. The report must seriously consider alternative hypotheses that might explain the association observed in case-control studies, and demonstrate that these cannot account for the findings. The present draft does not do this.

A broader issue, beyond the strengths and limitations of the studies on ETS and breast cancer, concerns how CalEPA addresses the issue of uncertainty. Irrespective of whether or not tobacco smoke causes breast cancer, the available data leave much room for uncertainty. Proponents of the concept that ETS exposure causes breast cancer argue that undue delay is more harmful to progress in tobacco control than is the opposite – concluding that ETS causes breast cancer when it is does not. I strongly disagree. I believe that a major policy reversal with respect to ETS and breast cancer would be far more damaging to the scientific credibility of tobacco control efforts – especially those based on other harmful effects of ETS - than a deliberative approach that acknowledges the limitations of the evidence currently available. Furthermore, as discussed below, I see no reason why CalEPA cannot draw attention to the potential link between ETS and breast cancer without concluding that the current evidence is sufficient.

General Issues

1) The discussion of the overall evidence on page 7-132, pp 1, lines 1-4 begins with the statement "..recent, primary, population-based case control studies (as well as three cohort studies) … have consistently identified elevated breast cancer risks for residential and occupational exposure overall, or in individual strata." This is misleading, in that it implies rapid accumulation of evidence supporting the hypothesis. In reality, Figure 7.4.4 indicates that eight of the ten studies published from 2000 to 2005 report relative risk estimates for

overall breast cancer in ETS exposed women near or below the null. The qualifier "or in individual strata" may be accurate, but subgroup findings do not constitute "consistent" support for the main hypothesis.

As seen in Figure 7.4.4, nine studies published from 1984 to 1999 reported RR estimates of 1.3 or greater for breast cancer in ETS exposed women. These studies drew attention to the possibility that ETS exposure might increase breast cancer risk. However, most studies conducted since the year 2000 have largely been unable to replicate the main finding. This temporal pattern should not be interpreted as rapidly accumulating support for the hypothesis. Rather, it is a reason to reexamine all of the data critically to identify possible sources of inconsistency.

2) OEHHA attributes the negative findings of recent studies to misclassification of ETS exposure, and inclusion of ETS exposed women in the referent group. However, at least two of the negative studies during the latter interval (Reynolds et al 2004 and Gammon et al 2004) excluded from the control group persons who reported ever living with a smoker. If there is in fact a dose-response increase in breast cancer risk with increasing duration of ETS exposure (as discussed below), the exclusion of women with any household exposure should allow higher breast cancer risk to be evident in women with long-term household exposure to ETS. However, in the Reynolds study, only active smoking is associated with breast cancer risk, and this association is unaffected by inclusion or exclusion of women with household ETS exposure from the referent group.

   If the absence of data on "important ETS exposures" accounts for the null findings of most of the studies published since the year 2000, it is not clear why all of the studies published before 2000 found a relatively strong association between ETS and breast cancer, even though six of these were also missing data on "important ETS exposures" (Table 7.4.1.B). The OEHHA report attributes the heterogeneity of the published studies to variations in the accuracy with which ETS exposure is measured. The report fails to consider inconsistencies in this hypothesis, and does not devote serious consideration to the possibility that the heterogeneous results may result from other unmeasured factors that are correlated with but separate from ETS exposure.

3) A central tenet of the OEHHA report is that a small amount of tobacco smoke (at levels consistent with ETS exposure) increases breast cancer risk, but that greater exposures, or at least those incurred from active smoking, do not further increase risk. The magnitude of the effect of passive smoking is said to be similar to that of active smoking. While this hypothesis may be biologically possible, it is not typical for a dose-response relationship, and requires further supporting evidence to convince skeptics. It may be that "OEHHA prefers to characterize non-linearity of the dose-response for breast

cancer to tobacco smoke as an observation, not a theory" (response to my 6th comment on the previous draft). However, unless there is good evidence to account for this observation, breast cancer researchers will continue to see the unusual dose-response relationship as an important limitation in the evidence.

a. The OEHHA report seems internally inconsistent with respect to the presence or absence of a dose-response relationship. Page 7-132, paragraph 2 argues that there is "a positive dose-response relationship [between breast cancer risk and] passive smoking". Table 7.4.1J presents data from seven studies supporting this view. Nevertheless, the null results of cohort studies published by Reynolds et al.(2004), Egan et al. (2000), and Wartenberg et al. (2000) are dismissed as invalid because they only measured ETS exposure in adulthood, not in childhood. If it is true that the duration of ETS exposure is important, then studies that assess the duration of exposure in adulthood should be able to detect increased risk associated with long term exposure.

b. The potential for recall bias and uncontrolled confounding is particularly great in case control studies in which the referent group is restricted to women who report no active smoking and no ETS exposure in either childhood or adulthood. These women generally constitute between 10% and 25% of potential controls and may or may not differ from other women on factors related to breast cancer risk (published data only provide information on all cases and all controls, not on this relevant subgroup). Although studies vary in the extent to which they control for covariates, none of the studies control for mammography (which the affects the age at which breast cancer is diagnosed as well as overall incidence); only the cohort studies control for post-menopausal hormone use. Some studies control for alcohol consumption only as "ever – never" and for reproductive factors only in broad categories. Women who report no ETS exposure may be more likely to work at home, to be relatively isolated, and/or to belong to special religious groups. All of these attributes may influence other factors related to breast cancer. However, none of the published studies provide information on the demographic and other characteristics of this subgroup that is reputed to be the only appropriate referent group.

4) The current draft still overstates the significance of currently available data on subgroup analyses, particularly with respect to genetic polymorphisms and gene-environment interactions. For example, page 7-145, lines 7-5 from bottom states that such analyses provide evidence for "..highly significant increased breast cancer risk associated with active smoking ". This overstates the importance of the data from Crouch et al. 2001. There is actually widespread skepticism about most published analyses of risk associated with low penetrance susceptibility alleles, because these findings have been difficult to replicate and it is unclear how to interpret *a posteriori* findings

from underpowered studies. It also seems specious that OEHHA characterize the conflicting findings regarding genetic susceptibility in studies of ETS and breast cancer as "diverse rather than conflicting" (response to my seventh comment on the October, 2004 draft). Whether one calls these "diverse" or "conflicting", they do not provide strong evidence in support of the hypothesis.

5) It can be argued that the subgroup of studies on premenopausal breast cancer deserves to be singled out, since most of these find relative risk estimates above 1.0 (Table 7.4.1.c and Figure 7.4.5). However, the data on premenopausal breast cancers derive largely from case-control studies (since breast cancer is much less common in pre- than in post-menopausal women). This downplays the evidence from the cohort studies even more than does the discussion of overall breast cancer risk. However, all of the concerns about recall bias and uncontrolled confounding, discussed above, are at least as applicable to the studies of pre- as of post-menopausal breast cancer. Furthermore, the issues of age at onset and age at exposure are separate and should not be conflated. For example, the timing of exposure is very important with respect to breast cancer risk from ionizing radiation. Women who are exposed to ionizing radiation during adolescence have a greater increase in breast cancer risk than those who are exposed at older ages. However, breast cancer is generally a "late effect" from ionizing radiation, and most of the increased risk occurs after menopause. Thus, considerations concerning age at exposure should be distinguished from issues concerning the age at onset of disease.

Specific comments

1) Page 7-103, pp 3, line 2: Change "several" to "at least 15". Also, in line 3, insert "since the previous OEHHA report" after "studies.

2) Page 7-103, pp 3, line 8: Change "accounted for other risk factors" to "accounted for a number of covariates that affect breast cancer risk or diagnosis":

3) Pages 7-128 and 7-131: The use of a log scale for the Y axis in Figures 7.4.4 and 7.4.5 makes the results seem more similar than they are. On a log scale, small relative risks appear to be larger than they are, and disproportionately large estimates appear much closer to the others. Although this is scientifically legitimate, it exaggerates the appearance of consistency in the eyes of a general audience.

4) Pages 7-129 and 7-131: Table 7.4.1.C and Figure 7.4.5 need footnotes clarifying that the Wartenberg et al. paper did not actually present results on premenopausal breast cancer) only on women less than age 50 at baseline, and that the relative risk estimates to two figures past the

decimal did not come from the publication. The actual source of these should be stated.

5) Page 7-132: PP 1, lines 1-4. This sentence overstates the support that "recent, population-based case control studies (as well as three cohort studies) provide for the hypothesis.

6) Page 7-133: The second paragraph states that "studies which include examination of peri-pubertal adolescent and prepregnancy/nulliparous exposures are preferable." This is true, provided that there is evidence that self-reports of ETS exposure in adolescence are reliable when collected in case-control studies, and that restricting the referent group to women who report no ETS exposure in adolescence is not introducing unrecognized biases.

Final comment

I believe that the disagreement between CalEPA and the great majority of breast cancer researchers can be avoided, if the report designates the evidence currently linking ETS and breast cancer as limited. This would not preclude the possibility that ETS and active smoking may affect breast cancer risk. It would not prevent CalEPA or tobacco control advocates from publicizing the issue. It would simply characterize the current information honestly and without exaggeration.

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11 March, 2004

R Krieger
Staff Air Pollution Specialist
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Dear Mr Krieger,

I am a statistician/epidemiologist who has been working in smoking and health for almost 40 years and have published widely on ETS. Although my work has been funded by the tobacco industry, I have contributed to governmental reports in the past. For example, I was acknowledged in the EPA report on ETS.

I have recently been sent a copy of the draft report "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003," and have received an invitation to attend a public workshop to discuss it. Unfortunately, I am unable to come over to California for the meeting, but I would like to make some comments. These are summarized in the attached note, "First comments on the Draft Technical Support Document relating to the Proposed Identification of ETS as a Toxic Air Contaminant" and enlarged upon in a number of published and unpublished review papers which are enclosed. The unpublished papers should all shortly be available on my website, www.pnlee.co.uk.

Yours sincerely,

Peter N Lee

Encs

First comments on the Draft Technical Support Document
relating to the Proposed Identification of ETS as a Toxic Air Contaminant

Author : P N Lee
Date: 11.3.2004

Part A Chapter 3

While I am glad that my review on cotinine[1] has been cited (on page V-54), have no objection to being referred to as a consultant with tobacco industry involvement, and have no problems with the conclusions of my work as summarized in the Draft review, I found it odd that the paper is cited as "P.N.Lee, 1999" when all the other references in the Draft do not give initials. A similar citation is made on page V-61 and, amusingly, on page V-78, the reference to my paper appears between Pirkle and Poore and not in its correct alphabetical order.

Part B Chapter 3. Development Toxicity : 1: Perinatal Manifestations

3.2 Fetal growth

The report considers that there is conclusive evidence of an effect of ETS on fetal growth. I disagree for reasons that are discussed in some detail in the enclosed review[2]. That review includes results from a large number of relevant epidemiological studies. The authors of the Draft chapter may find it useful to check whether, in Tables 1-3, I cite any papers they may have missed.

Part B Chapter 4. Developmental Toxicity: II. Postnatal Manifestations

4.1 SIDS

The report considers that there is conclusive evidence of an effect of ETS on SIDS. I disagree for reasons that are discussed in some detail in the enclosed review[3].

Part B Chapter 6. Respiratory Health Effects

6.2.1 Asthma induction

My colleagues and I are in the process of conducting an extensive review of the evidence on asthma induction and ETS. Currently, we have data from some 160 studies on our database and hope to analyse it in a month or

two. When our conclusions are drawn, I should be able to make the report available.

Part B Chapter 7. Carcinogenic Effects

I have concentrated my comments on the data for adults, as I have not recently reviewed the data on childhood cancer. In any case, the conclusions reached in the Draft are not very different from those from my 1998 review on childhood cancer[4].

As regards cancer in adults, I have recently reviewed the evidence extensively. The relevant material for lung cancer is described below, while that for other cancers was reviewed in a published paper in 2002,[5] since updated in an unpublished review.[6] Copies of these are enclosed.

Below I present my comments on a site-by-site basis.

7.1 Total cancer risk in adults and ETS

A recent relevant study has been missed.[7]

7.2 Lung Cancer and ETS

I find it extremely depressing that no mention whatsoever is made of the series of five papers that my colleagues John Fry, Barbara Forey and I published[8-12] in Indoor + Build Environment in reply to the review paper by Hackshaw *et al*[13] in the BMJ. These provide extremely detailed support for our view that the dose-response relationship between lung cancer and ETS exposure may be plausibly explained by (i) bias due to smoking misclassification, (ii) confounding by fruit, vegetables, dietary fat and education, (iii) correction of errors in one published study, (iv) inclusion of results from all pertinent studies and (v) restricting attention to those studies that have adjusted for age. A set of reprints of the five papers is enclosed.

I also feel the report lacks meta-analyses. I enclose up-to-date meta-analyses[14] based on data summarized in another document,[15] also enclosed.

7.3.1 "Nasal sinus cancer"

The report mistakenly considers cancers of the nasopharynx under this heading. The two cancers should be kept separate. The evidence for nasopharyngeal cancer is highly variable and most unconvincing, as described in my unpublished review of "the epidemiological evidence on environmental tobacco smoke and cancers other than the lung."[6] As is evident from that review, there is another relevant study that has been missed in the draft.[16]

The evidence on nasal sinus cancer is in fact no more than it has been for a number of years. Reasons why the evidence seems inconclusive are given in my review.[6]

7.3.2 Cervix cancer and ETS

Two relevant studies of ETS and cervix cancer have been missed.[7,17] For one of these[17] the title concerns lung cancer but relevant data on cervix cancer are included. See my review[6] for a summary of my views. We agree the data are inconclusive.

7.3.3 Bladder cancer and ETS

There is a recent study on this not considered in the Draft.[18] The evidence remains not even suggestive of a relationship.[6]

7.4.1 Breast cancer and ETS

In view of the report of the Collaborative Group on Hormonal Factors in Breast Cancer[19] that concluded, based on reanalysis of data from 53 studies, that "smoking has little or no independent effect on the risk of developing breast cancer," it would seem extremely unlikely that ETS might cause breast cancer. For reasons discussed in my review,[6] the direct epidemiological evidence that it does so is extremely unconvincing. I regard it as quite amazing that the Draft should reach the conclusion that ETS definitely causes breast cancer.

I believe that four relevant studies have been missed out.[20-23] Note that when all the relevant data are in, fixed effects meta-analysis shows no

association, with a relative risk estimated as 1.06 (95% CI 0.99-1.14). See my review[6] for details.

7.4.2 Stomach cancer and ETS

Two relevant studies have been missed.[17,24] The evidence is not suggestive of a relationship.[6]

7.4.3 Brain cancer in adults and ETS

Two relevant studies have been missed.[25,26] The overall evidence is inconclusive.[6]

7.4.4 Leukemia in adults and ETS

One relevant study has been missed.[27] It showed no association.

7.4.5 Lymphoma in adults and ETS

One relevant study has been missed.[27] It showed no association.

Other cancers in adults and ETS

As my review[6] demonstrates, there are also some limited data for a range of other cancers.

Part B Chapter 8. Cardiovascular health effects

I disagree with the Draft's conclusions about ETS and heart disease for reasons that are discussed briefly in the enclosed unpublished review[28] which is concerned mainly with the epidemiological evidence, and at more length in an earlier published review,[29] which deals with both the experimental and the epidemiological evidence.

As my unpublished review[28] makes clear, there are a number of papers on the epidemiology of ETS and heart disease that appear to have been missed in the Draft. There are four published after 1997 that are relevant.[30-33]

The Draft would improve from having some up-to-date meta-analyses. These are given in an enclosed document.[14]

References

1. Lee PN. Uses and abuses of cotinine as a marker of tobacco smoke exposure. In: Gorrod JW, Jacob P, III, editors. *Analytical determination of nicotine and related compounds and their metabolites*. Amsterdam: Elsevier, 1999;669-719.

2. Lee PN. *ETS and birthweight*. 2003. www.pnlee.co.uk

3. Lee PN. *ETS and sudden infant death syndrome*. 2002. www.pnlee.co.uk

4. Thornton AJ, Lee PN. Parental smoking and risk of childhood cancer: a review of the evidence. *Indoor Built Environ* 1998;**7**:65-86.

5. Lee PN. Environmental tobacco smoke and cancer of sites other than the lung in adult non-smokers. *Food Chem Toxicol* 2002;**40**:747-66.

6. Lee PN. *Epidemiological evidence on environmental tobacco smoke and cancers other than the lung*. 2003. www.pnlee.co.uk

7. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, *et al*. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control* 2001;**12**:797-802.

8. Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. I. The dose-response relationship with amount and duration of smoking by the husband. *Indoor Built Environ* 2000;**9**:303-16.

9. Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. II. Adjustment for the potential confounding effects of fruit, vegetables, dietary fat and education. *Indoor Built Environ* 2001;**10**:20-39.

10. Lee PN, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. III. Adjustment for the biasing effect of misclassification of smoking habits. *Indoor Built Environ* 2001;**10**:384-98.

11. Lee PN, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. IV. Investigating heterogeneity between studies. *Indoor Built Environ* 2002;**11**:4-17.

12. Lee PN, Fry JS, Forey BA. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. V. Overall conclusions. *Indoor Built Environ* 2002;**11**:59-82.

13. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997;**315**:980-8.

14. Lee PN. *Meta-analyses of the epidemiological evidence relating ETS to lung cancer and heart disease*. 2004. www.pnlee.co.uk

15. Lee PN. *ETS and lung cancer meta-analyses*. 2004. www.pnlee.co.uk

16. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer* 1990;**45**:1033-9.

17. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* 1999;**28**:824-8.

18. Zeegers MPA, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control* 2002;**13**:83-90.

19. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58515 women with breast cancer and 95067 women without the disease. *Br J Cancer* 2002;**87**:1234-45.

20. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, *et al.* Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res* 1996;**87**:1001-9.

21. Furberg H, Millikan RC, Geradts J, Gammon MD, Dressler LG, Ambrosone CB, *et al.* Environmental factors in relation to breast cancer characterized by p53 protein expression. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:829-35.

22. Rookus MA, Verloop J, de Vries F, van der Kooy K, Van Leeuwen FE. Passive and active smoking and the risk of breast cancer [Abstract (SER)]. *Am J Epidemiol* 2000;**151(Suppl)**:S28.

23. Woo C, Davis D, Gravitt P, Skinner H, Ward C, White JE, *et al.* A prospective study of passive cigarette smoke exposure and breast cancer [Abstract (SER)]. *Am J Epidemiol* 2000;**151(Suppl)**:S72.

24. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 1984;**13**:680-90.

25. Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *J Epidemiol Community Health* 1996;**50**:442-6.

26. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* 1997;**8**:5-12.

27. Hirayama T. Passive smoking and cancer: an epidemiological review. *GANN Monograph on Cancer Research* 1987;**33**:127-35.

28. Lee PN. *Epidemiological evidence on environmental tobacco smoke and heart disease*. 2004. www.pnlee.co.uk

29. Lee PN, Roe FJC. Environmental tobacco smoke exposure and heart disease: a critique of the claims of Glantz and Parmley. *Hum Ecol Risk Ass* 1999;**5**:171-218.

30. McElduff P, Dobson AJ, Jackson R, Beaglehole R, Heller RF, Lay-Yee R. Coronary events and exposure to environmental tobacco smoke: a case-control study from Australia and New Zealand. *Tob Control* 1998;**7**:41-6.

31. Iribarren C, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. *J Epidemiol Community Health* 2001;**55**:721-8.

32. Pitsavos C, Panagiotakos DB, Chrysohoou C, Tzioumis K, Papaioannou I, Stefanadis C, *et al*. Association between passive cigarette smoking and the risk of developing acute coronary syndromes: the CARDIO2000 study. *Heart Vessels* 2002;**16**:127-30.

33. Chen R, Tunstall-Pedoe H. Coronary heart disease in relation to passive smoking by self report, serum cotinine and their combination: Scottish MONICA study [Abstract]. Society for Epidemiologic Research 36th Annual Meeting, Atlanta, Georgia, June 11-14, 2003. *Am J Epidemiol* 2003;**157(Suppl)**:S27.

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19 February 2004

Ms Janette Brooks
Chief, Air quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street/ P.O. Box 2815
Sacramento, California 95812

Dear Ms Brooks

RE: EPA of California report on the health effects exposure to tobacco smoke.

I have a long standing interest in a possible causal relationship between active and passive exposure to cigarette smoke and breast cancer. My most recent publication was:

Burton R C, Sulaiman N. *Cigarette smoking and breast cancer: is a real risk emerging?* Medical Journal of Australia 2000; 172:550-552.

In that review I concluded that a causal association had not been established but was both biologically and epidemiologically plausible and likely.

I have read carefully and with interest the relevant pages on breast cancer and cigarette smoke exposure contained in the first 11 pages of Chapter 7 and pages 7-91 and 7-155 of the proposed revision to your 1997 report, which I obtained from the web address: http://www.arb.ca.gov/toxics/ets/dreport/dreport.htm.

I agree with the conclusion that the totality of findings now provides evidence of a causative association between both active cigarette smoking and exposure to environmental tobacco smoke and breast cancer. The studies published since I reviewed the literature are of high quality, and taken together with the older literature support the conclusion that has been reached in that report.

In particular, the risks associated with cigarette smoke exposure when the breast is undergoing rapid cell division should be emphasized. That is, during childhood through puberty and in first pregnancy. I would be pleased to provide further commentary should you require it.

Kindest regards.

Yours sincerely,

Robert Burton

Robert Charles Burton
Strategic Leader
International Union Against Cancer (UICC)
Head, Cancer Strategies Group
Commonwealth Government of Australia
Senior Advisor
National Cancer Control Initiative (NCCI)

cc: Ms Isabel Mortara, UICC
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Ms. Janette Brooks
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California Air Resources Board
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Dear Ms. Brooks,

The Division of Cancer Control and Population Sciences has reviewed Chapter 7 on Carcinogenic Effects in "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant", Draft Report Part A and B, December 2003 and is submitting the attached comments on the report.

Thank you for the opportunity to review this important document. If you have any questions about the attachment, feel free to contact Dr. Deborah Winn, Acting Chief, Clinical and Genetic Epidemiology Research Branch, Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute. She can be reached at 301-594-9499, fax 301-435-5477, and email at winnde@mail.nih.gov.

Sincerely,

Deborah M Winn for

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Comments on Chapter 7 Carcinogenic Effects in "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant", Draft Report Part A and B, December 2003 by the California Environmental Protection Agency

From the

Division of Cancer Control and Population Sciences
National Cancer Institute
March 2004

The California EPA's report on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant provides an excellent discussion of findings on the health effects of ETS. The Division of Cancer Control and Population Sciences of the National Cancer Institute appreciates the opportunity to review and comment on this report. The authors of the report should be congratulated on this achievement. The California EPA's previous report has served as an authoritative reference document on ETS and health effect, and this new report is likely to become widely read and cited. Two important changes in the new report are the designation of ETS as causes of nasal and breast cancers. This is in contrast to the findings of the International Agency for Research (IARC) in 2002. Although the IARC report in the monograph series Evaluation of the Carcinogenic Risks to Humans, Tobacco Smoke and Involuntary Smoking, Volume 83 is not yet published in book form, the summary conclusions are available at the agency's website: http://monographs.iarc.fr/htdocs/indexes/vol83index.html. In view of the differences between the conclusions of two reports and the public health implications of the new designations by the California EPA of ETS as causal factors in the etiology of particular cancers, the National Cancer Institute, part of the National Institutes of Health, strongly recommends the appointment by the California EPA of an expert panel representing the appropriate disciplines to review and to come to a consensus on the evidence on ETS and cancer.

Some specific comments on Chapter 7 Carcinogenic Effects:

Section 7.3.1 Nasal sinus cancer

The studies listed under nasal sinus cancer appear to be for nasopharyngeal cancer, a different anatomic site than nasal cancer, a term that typically refers to cancers of the nose and paranasal sinuses.

Section 7.4.1 Breast Cancer

More weight should be given to the recent published findings from cohort studies in view of their large size and ability to clearly establish exposure as occurring before recognition of the cancers.

The meta-analysis from the Collaborative Group Study of Breast Cancer, Alcohol, and Smoking used a simplistic characterization of active smoking in their analysis - ever/never and current/ex-smoker - however, it is not clear why this variable would be considered by the California EPA authors as "poor quality".

Section 7.4.1.3 Active smoking and breast cancer.

The first paragraph that preceeds the discussion of individual studies appears to be a partial summary, but it does not synthesize the information and may be misleading. For example, it appears that positive findings that appear only in a subgroup are not labeled as such. The Egan study is said to show an association in either active or former smokers. However, that study showed no overall association of smoking and breast cancer among current smokers (RR=1.04) or ex-smokers (1.09) and so the authors probably were referring to active and former smokers among a subset of the women.

This section needs a synthesis that assesses the body of epidemiological evidence. Since the findings for the active smoking section presumably are included to provide evidence about the plausibility of the findings for passive smoking and to set the stage for discussions about consistency with ETS findings, there probably should be a synthesis section for each active smoking section with updated information/studies. The synthesis should clearly distinguish overall findings for smoking and breast cancer from findings in specific subgroups.

Section 7.4.1.4. ETS and breast cancer.

Section 7.4.1.5. A new study that could be included here is: Gammon MD et al., Environmental tobacco smoke and breast cancer incidence. To be published in Environmental Research in 2004, but available now through Science Direct.

The citation to Terry et al., 2002 on page 7-122 is incorrect. This study does not address passive smoking and breast cancer, only active smoking.

There is a reference to a paper by Zhao in 1999 in Table 7.4F. However, this study is not described in text and the reference does not appear in the list of references.

Section 7.4.1.6. This section is labeled as a summary of the evidence regarding ETS, but it focuses only on the possible explanations of findings reported in the previous CalEPA report and does not address findings since then. Have the limitations to the interpretation of the findings in the previous CalEPA report been fully addressed in the more recent studies?

Overall risks associated with passive smoking and dose response relationships should be summarized, then focus on subsets (e.g., pre and post -menopausal), providing risks for the subset and, where available, dose-response relationships for that subset.

Section 7.4.1.7 Consistency. Starting on page 7-136
This section addresses the qualities of the most recent studies, not the consistency among them. To address consistency this section should include an evaluation of agreement among the studies of ETS, including across subgroups defined by biological characteristics (e.g., menopausal status) as well as the consistency with findings for active smoking as well as the consistency of findings within studies that examined both active and ETS.

Section 7.4.1.7. Strength and specificity. Recommend addressing overall risks associated with passive smoking and the dose-response relationships curve overall, then focus on subsets of women (e.g. pre and post menopausal) providing the risks for the subset and the dose response for that subgroup, if available. This is an important distinction because a finding that is homogenous across subgroups and shows a dose response relationship must have a different biological mechanism than one that is confined to women with particular biological characteristics (e.g., particular types of tumors, women with particular biological characteristics such as menopausal status).

7.4.G. Add a table on post-menopausal findings. This would be useful for assessing consistency of findings.

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March 16, 2004

Ms. Janette Brooks
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Comments on Draft Technical Support Document for the Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant Dated December 2003

Dear Ms. Brooks

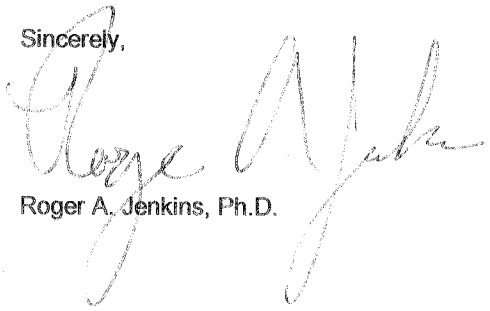
Attached herewith are my comments on the initial draft report mentioned above. Since my expertise is in the area of exposure science and analytical chemistry, I have provided comments only on Part A of the Report. In order to provide you some perspective regarding my comments, I have also included a copy of my current Curriculum Vita.

In the interest of openness, I am disclosing to you that I was retained by Womble Carlyle Sandridge & Rice (WCSR), a law firm in Winston-Salem, NC, that represents R.J. Reynolds Tobacco Company, to perform a detailed analysis of the Draft Report and provide written commentary to you. However, no one from WCSR or RJ Reynolds reviewed any of these comments, nor discussed the substance of them with me, prior to the comments being filed with you.

For your convenience, I have enclosed a disk (yes, I know, old fashioned technology) with PDF's of both my CV and comments, should you decide to distribute these materials to your staff. The files have been scanned with anti-virus software and are clean.

Thank you for the opportunity to comment on this important public issue. I look forward to the next step in the process.

Sincerely,



Roger A. Jenkins, Ph.D.

Comments on California Air Resources Board Report:

Draft Technical Support Document for the
"Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"

December, 2003

Comments by Roger A. Jenkins, Ph.D.
Submitted March 17, 2004

Address questions to:

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SUMMARY COMMENTS

The new report on the "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" is an attempt at a thorough review of new scientific literature with regard to emissions of, exposures to, and health effects from environmental tobacco smoke (ETS). In some sections and subsections, the report provides a solid analysis. However, in general, the Draft Report is woefully inadequate, and needs substantial revisions before it should become a matter of record. After reviewing the document, I have three major criticisms of and concerns about the document.

First, for its analysis of exposures of Californians to ETS, it relies too heavily on indirect indicators of exposure to ETS and its components, such as time spent around smokers, and employs examples of potential exposure scenarios, and attempts to model exposures from such, instead of using data available from the scientific literature that measures exposures directly. In addition, after having used surrogate measures of exposure, there is no attempt made in the Report to confirm the accuracy of predictions by using previously published data.

Secondly, there is no perspective provided in the report. For a government agency to release such a document without providing perspective that the public can use to interpret the data is unconscionable. For example, much is made of the emissions of certain components, such as carbon monoxide, from cigarettes. While 1907 tons per year of CO may sound like a lot, in fact, it is the equivalent amount of CO emitted from a few thousand of California's millions and millions of automobiles and heavy vehicles. To seek to regulate smoking in the basis of emissions into the ambient environment would appear ludicrous at best, and threatens the credibility of the entire Report.

Third, evidence is provided in the report to indicate that the constituents of ETS begin to react and decompose within short periods of time following their emission into the ambient environment. Clearly, ETS in ambient air in sunlight for any important length of time is no longer ETS. And yet the Report provides no justification or rationale as to why the use of existing regulations that establish safe concentrations of many of the components on interest in ETS is not an appropriate approach. ETS is treated like some sort of nefarious elixir that lasts forever, and yet the data provided in Section VI shows that this is clearly not the case. That such is not presented provides the perception that the authors of the report are biased and have other agendas beyond the examination of ETS as a toxic air pollutant.

Finally, perhaps the most egregious transgression of the Draft Report is that of its clearly incomplete and sometimes biased reviews of the scientific literature. This bias leads to statements that are simply unsupportable by the scientific literature and provides for an unwarranted tone of "advocacy" that threatens the entire credibility of the draft report. That the Draft Report selectively ignores key scientific studies, or spends pages discussing criticisms of only selected studies, while ignoring criticisms of other similar studies provides for a sense of bias on the part of the authors of the Report. If these errors are permitted to stand in the final document, the report is likely to be dismissed by anyone who is not an anti-smoking activist.

Specific comments on Sections.

Chapter 3 Chemical and Physical Properties of ETS

This is a reasonably succinct summary of major properties of the complex mixture known as ETS. There are some errors and mis-interpretations that need to be corrected.

Page III-2,

The statement: " ....With few exceptions (e.g., hydrogen cyanide and organic acids), sidestream smoke contains greater mass emissions as compared to mainstream smoke (Jenkins et al., 2000) on a per cigarette basis....." requires some additional explanation. The reason why SS smoke contains more material typically is because greater mass of tobacco is consumed during smoldering, compared with active puffing. However, many of the more basic components exist in even greater relative concentrations because combustion conditions (air flow and fuel consumption rate) favor the production of more basic species.

Page III-3

In the top paragraph, the text fails to make clear that most of the mainstream smoke that contributes to ETS is exhaled mainstream, that has been diluted in the lungs of the smoker, aged, and scrubbed of some of its more soluble gas components.

Page III-4

Last Paragraph The monograph to which the citation Jenkins et al, 2000 refers did not involve any new experimental work. No measurements were made.

Page III-5

First Paragraph: The statement " ....In general, highly concentrated mainstream smoke has constituents preferentially distributed in the particle phase region (Jenkins et al., 2000). Smaller sidestream smoke particles in the ambient air can be inhaled deeply into the lower respiratory tract, where they can have a deleterious health effect....." suggests a nearly binary distribution of tobacco smoke droplets (particles) between SS and MS smoke. However, given the huge breadth of the distribution, the distributions of both smokes should be considered as continuums. *Also, the suggestion that somehow the slightly smaller particle size distribution of SS may result in more deleterious health effects is not supported in the scientific literature.* While there may be differences that are statistically different in the distribution parameters, such as the mass median aerodynamic diameter, it is not altogether clear that there is a true functional difference in the two distributions. If there is new evidence of this, then the authors need to cite such.

Chapter IV Production, Uses, Sources, Emissions, And Smoking Trends

In the discussion of emissions of cigars and cigarettes, there is a serious lack of perspective provided to the reader to evaluate the relative importance of the emission.

Page IV-2

Last Paragraph The work described in Djordjevic et al (2000) represents an important contribution to the scientific literature, but it is unclear how a discussion of the carbon monoxide in *mainstream cigarette smoke* bears on the discussion of ETS emissions. This is particularly true for CO, virtually all of which is scrubbed from MS smoke once it is held in the smoker's lungs for a few seconds.

Page IV-7

Table IV-3 presents a summation of estimates of statewide emissions of three components of environmental tobacco smoke, respirable suspended particulate matter, nicotine and carbon monoxide.

The lack of any data comparing this to the same emissions from other sources is a serious flaw in the report, since no perspective is provided for the reader. For example, how do these CO emissions compare with those of the motor vehicles in the state? According to the EPA, each typical automobile emits 575 pounds per year of CO. So it would take less than 7000 cars to emit the same amount of CO that all the smokers emit in California. Compared to the 15 million or so cars in the State, such a trivial comparison threatens to undermine the potential importance of a report such as this. In terms of nicotine, no comparative data is provided. California has a major agricultural industry. Nicotine is present in the flesh of tomatoes, peppers, eggplant, and all the vegetables of the solanaceous family. The amount of nicotine that is emitted by all crops is not provided so that the reader can have some perspective. The levels of RSP that are emitted by the smoking of cigarettes, something like 365 tons per year, seems pretty insignificant compared to other sources across the State. The report needs to provide data with respect to power plant emissions, emissions from vehicular traffic, including releases of RSP from the wearing of break linings and exhaust systems, and the agricultural business within California. Without such data, the report loses much of the respect that it should have, and appears to be unnecessarily advocative.

Furthermore, the report is unclear as to how the emission levels were calculated. When asked about this in the March 15, 2004 review of the Draft Report, the team responsible indicated that the emissions were calculated assuming that all the cigarettes smoked in California would contribute to ambient levels of air pollutants. For this assumption to be rational, either all cigarettes smoked in California would have to be smoked outdoors, or all of the components of smoke generated indoors would have to find their way to ambient air with no losses, either through reaction or deposition on inside surfaces. Since neither of these assumptions are rational, the estimate needs to be corrected for realistic circumstances. Otherwise, this calculation will have no credibility.

Chapter 5 Exposure to Environmental Tobacco Smoke

The manner in which the Chapter is written gives the appearance of placing greater reliance on modeling studies of exposure, rather than relying on direct measurement of exposure. If there was no data as to personal exposure to ETS, such might be understandable. However, such is clearly not the case. However, the Report ignores key available data that is California-specific, and appears to cherry-pick studies for inclusion without substantial, factual information as to why certain studies were ignored. The Chapter appears to place a great deal of reliance on modeling studies conducted in single environments that have been manipulated, and gives lesser weight to studies of measured personal exposure.

Page V-4

There is a discussion as to "exposure to smokers" by considering the time spent around smokers. However, no data is presented to support the contention that time spent around smokers, or the detection by the human that they have been exposed to ETS, results in exposures that are relevant from a clinical or health standpoint. Based on what we know about dispersion of gaseous molecules, one can make the argument that everyone in the state is "exposed" to some of the molecules of ETS 24 hours per day, seven days per week. In many cases, it may be difficult to measure, because the concentrations of the molecules would be so small. However, everyone IS exposed.

The Report fails to mention the fact at this point that strictly speaking, "exposure" is the product of time and concentration of material to which one is exposed. To discuss "time" of exposure only addresses one half of the exposure equation. Whether or not an individual is "exposed" is really irrelevant. The more important question is: how many individuals have exposures (the products of concentration and time) that are clinically significant? Let me draw from a personal example. I typically jog through our

neighborhood about 5 – 6 days per week. Since I jog in the early evening, there are a fair number of vehicles that pass me on the streets. I have a pretty sensitive olfactory system, and I can smell tobacco smoke at pretty low levels. In fact, I can smell it when smokers drive by in their cars, even with the windows rolled up. OK, if I can smell it, I KNOW I am getting exposed. However, is their a single physician willing to get up and say that such an exposure is truly damaging to my health, or even the cumulative effect of all the exposures I have received in the 15 years of jogging in this subdivision has any sort of clinical significance? ***To simply say that a person is exposed provides no useful information, because no perspective on the degree of exposure is provided.***

Page V6

The comment is made that solanesol can not be a good marker for ETS outdoors because it degrades in sunlight. Well, so do many other ETS constituents. Based on National Academy of Sciences criteria for good markers, it would sound like solanesol would do a good job tracking those constituents that degrade in sunlight. Also, it is true that solanesol levels can be low, but one can adjust sampling times or sample collection flow rates to compensate for such. It is true that there are no good commercially available standards for 3-EP. However, under standard protocols for analysis of nicotine and 3-EP, 4-EP elutes at essentially the same time and has been used by several laboratories for a standard.

Page V7

The new CARB study is introduced. However, the study appears to focus solely on nicotine, and as such, is subject to the limitations of this marker, which are not acknowledged in the material provided. Also, very high flows are used for sampling through large XAD-4 cartridges. Has this sampling approach been validated? Clearly, the fact that ***this study has not been reported in the peer-reviewed scientific literature*** needs to be acknowledged so that readers and scientists can weight its value accordingly, relative to the host of other exposure studies that have been through peer-review.

Also, several peer-reviewed studies have clearly demonstrated that because of its highly absorptive nature, nicotine can remain in the air hours or days after smoking has ceased. It does not appear that the Report acknowledges this limitation of nicotine as a marker.

Page V-9

Given the discussion in Chapter VI (see below), that acknowledges the degree of dilution/dispersion of ETS, interaction with UV light and other contaminants, discussion of "ETS" in ambient air, after a significant amount of time has passed, seems incongruent with the findings of Chapter 6. The authors of the Report present no supporting data to indicate that ETS survives with most of its primary constituents intact for any length of time. Such provides the serious impression on the part of the reader that "one hand does not know what the other is doing" in this Report. As such, such an inconsistency threatens the credibility of the entire Report.

Also, the Report begins a discussion of modeling of ETS concentrations in different scenarios. Modeling can be a useful approach in the absence of direct measurements. However, direct measurements are straightforward to conduct, and modeling can suffer from focus on one or two experiments and over-extrapolation of the data.

Page V-10

Near the bottom of the page, the statement is made that other sources of RSP contribute much less to indoor levels of RSP than does ETS. However, no data is cited to support this claim, except ANOTHER

CARB report on ETS. In addition, the comment ignores the wealth of scientific, peer-reviewed data which indicates that for most exposures of humans, in all but the most tobacco-smoke polluted environments, ETS contributes substantially less than half of the RSP. (See Jenkins et al, 2000, cited in the Report.) It is easy to determine the relative contribution of ETS if one measures solanesol levels in indoor air.

Page V-13

I believe it is here that the report performs an analysis of ETS concentration measurements in indoor air in California and elsewhere. Interestingly, the report ignores the data obtained from the so-called 16 Cities Study (Jenkins et al, 1996) in which Fresno, *a California city*, was one of the Cities in which monitoring was conducted. The data has been available for the entire study, segregatable by city, for years through the Sapphire Group (eg. Graves et al, 2000), and yet, the authors of this report chose to ignore this key piece of data. For example, 55 subjects in Fresno reported being exposed to the smoke of 1 or more cigarettes. Respirable suspended particulate matter (RSP) 24 hour time weighted average (TWA) concentrations ranged from 3.9 – 190.1 $\mu g/m^3$. 24-hr TWA nicotine levels ranged from 0.0 – 5.66 $\mu g/m^3$. To ignore such relevant data in the Report is inexcusable.

Page V-16

Why the authors would use the Graves et al (2000) manuscript to summarize the results of the so-called 16 Cities Study (Jenkins et al, 1996), when the Graves study focuses on ***non-smoking*** workplaces, is not justified in the text. Why not cite to the original study (Jenkins et al, 1996), that segregates data according to both smoking and non-smoking workplaces, or the derivative manuscript that specifically focuses on data analysis of workplace exposures (Jenkins and Counts, 1999)? Also, focusing on the Graves et al (2000) data presentation results in a data analysis that is grossly in error, and such errors give the impression of biased data analysis, which detracts from the entire report. For example, a claim in the Report is made that " ... results are somewhat low relative to other similar studies ...." However, no supporting data is provided to substantiate the claim. In fact, the comparison of mean 16 hour TWA away from work levels in smoking homes for RSP and nicotine for the 16 Cities Study (Jenkins et al, 1996), 44 and 2.71 $\mu g/m^3$, respectively, compares quite closely to that reported by Leaderer and Hammond (1991) of 44.1 and 2.17 $\mu g/m^3$.

Secondly, the Report indicates that demographics unrepresentative of the US population are responsible for lower exposure concentration levels. However, the Report fails to cite any other manuscripts where demographic data was reported for the subjects and fails to criticize any other studies, such as the aforementioned Leader and Hammond work, for skew demographics. (In the case of the Leader and Hammond 1991 manuscript, all the data was obtained from 47 homes in two counties in New York State.) The report fails to cite any other manuscript in the scientific literature that reports direct personal exposure to ETS that achieved a truly demographically representative sample of the US population. Such biased data analysis provides an unnecessarily advocative tone to the Report. In addition, the 16 Cities Study is criticized for having a *lower population of smokers* than the US population at large. And yet the study is clear that it only focused on non-smokers and that smokers were specifically excluded from the population studied. The authors of the CARB report need to clarify their statements.

Page V-17, Table V-6

This table completely ignores several important studies, including ***14*** from Keith Phillips' team at Covance Laboratories (see references), Sterling et al, (1996), Trout et al, (1998), Maskarinec et al, (2000),

Jenkins et al, (2001). Such omissions gives the perception, incorrectly or otherwise, that the authors of the report are "cherry-picking" the data that they are providing to decision makers.

Page V-22

In the discussion of RSP studies performed in California, the Report has ignored again the publicly available data on Fresno produced from the 16 cities Study (Jenkins et al, 1996). For example, for 27 Fresno subjects in truly smoking homes, RSP exposures ranged from 40 – 3324 $\mu g\text{-}hr/m^3$. Additional data is provided on ultraviolet absorbing particulate matter (UVPM) and fluorescing particulate matter (FPM) as markers for combustion derived particles, and solanesol-derived particulate matter (Sol-PM) as a marker for tobacco derived particulate matter.

Page V-23

In a discussion of studies of RSP outside California, the Report devotes an entire paragraph to an unpublished, un-peer reviewed study reported on James Repace's web site. This study employed a nephelometer (MIE Personal DataRam (pDR)1200) for analysis of RSP concentrations. However, the Repace report ignores a body of data in the scientific literature that indicates that such nephelometers over-report actual concentrations. Indeed, in a recently published peer-reviewed manuscript (Jenkins et al, 2004), the pDR has been shown to over-report the concentration of ETS RSP by a factor of 2. That the CARB Report does not mention the lack of disclosure of over-reporting illustrates the problem of over-reliance on non-peer reviewed data. It also detracts from the potential credibility of the entire report.

Page V-24

Table V-8 This table ignores several other published studies (Phillips et al, etc). In addition, it cites the Graves et al (2000) manuscript from the 16 Cities Study, (that focuses on non-smoking workplaces) and references its UVPM data, when RSP data is cited in the original study (Jenkins et al, 1996).

Page V-27

In the discussion of other ETS constituents, all of the literature on levels of 3-ethenyl pyridine seems to have been ignored. For California, this would include the Fresno data from the 16 Cities Study, and for elsewhere, would include both the series of studies from Phillips et al, Georgiadis et al (2001) on ETS and PAH's, and the work by Heavner et al (1996) on VOC's in homes. Instead, the Report focuses on an unpublished, non-peer reviewed study by Repace.

Page V-30

Modeling Studies

There is too much reliance on the use of the term: "exposed" to ETS. The criteria for what constitutes exposure is not adequately defined in this part of the report, and yet there is clearly a huge range of potential exposure magnitudes from a given observation. For example, suppose two individuals report "exposure" to the smoke of one cigarette. One of them lives in a small house trailer with a spouse, while the other walks past a smoker as he enters an airport. Both of these individuals have been "exposed." But the true exposures (ie, the product of concentration and duration) of the two individuals may vary by a factor of 100 or more. Frankly, to use the term "exposed" without reporting other factors is both potentially misleading and certainly obfuscative.

Modeling studies should only be relied upon where there is an absence of personal exposure data from which to draw. The statement cited by the report regarding the amount of acrolein inhaled by the US population annually is so bizarre and off-target as to be embarrassing that the Report authors chose to include it. It may be that Americans inhale a total of 260 kg of acrolein per year, but they also eat something on the order of 7 billion kg of fat per year. This sort of statement provides the perception that the Report is unnecessarily advocative.

Page V-31

The discussion of a National Ambient Air Quality Standard applied to this issue seems inappropriate, since the air in at least 50 % of private residences would violate such a standard routinely, even if no smoking was occurring.

Also, in the modeling discussions, there is no comparison made to direct measurements of either concentration or exposure. That is not to say that models can not be accurate. It is just that some effort needs to be made to compare with real data where available. For example, an analysis of data obtained in the 16 Cities Study for Fresno, CA for subjects living in homes where cigarettes were observed to have been smoked, median15.5 hour personal exposure TWA concentrations for RSP were 21 $\mu g/m^3$, and the 80^{th} percentile value was 42.2 $\mu g/m^3$. 95^{th} percentile value was 88.3$\mu g/m^3$.

The Repace presentation at the 2000 ISEA meeting is cited. Such is fine. However, if presentations are to be cited in this document that have not been published in the peer-reviewed scientific literature, then a) they need to be referenced in the text as such, and b) all presentations presented relevant to the subject matter must be cited and discussed. Many, many presentations relevant to ETS concentrations have been reported at scientific meetings in the last ten years, including the same meeting in which the aforementioned presentation was made, but their results have not been included in the data analysis. Such gives the perception that the authors of this section of the report are cherry picking the studies that provide results that suit whatever agenda they may have.

Summary of Indoor Data

Page V-33

The statement that RSP levels in offices and restaurants where smoking is permitted range from 100 – 400 $\mu g/m^3$ is not supported by any literature cited in the text (ie, there are no citations). Furthermore, it is incongruent with reported scientific literature. For example, in the work by Maskarinec et al (2000) cited in the Report, the median RSP concentration for non-bar areas in restaurants and bars was 66 $\mu g/m^3$ and 82 $\mu g/m^3$, respectively. 80^{th} percentile levels of RSP were 117 and 228 $\mu g/m^3$ respectively. In a manuscript not cited by the report, but clearly relevant (Jenkins et al, 2001), 72 samples acquired in 26 offices and cubicles in one large office building where smoking was unrestricted exhibited median and 80^{th} percentile RSP concentrations of 29.9 and 46.1 $\mu g/m^3$, respectively. Detailed thorough reviews of the scientific literature (eg, Jenkins et al, 2000) have usually demonstrated median or mean RSP levels in smoking offices to be less than 100 $\mu g/m^3$.

Citations on this page are inadequate or confusing. For example, Repace (in press) is cited, but there is no citation in the list of references provided that a particular manuscript has been accepted for publication in a peer reviewed journal but not yet published. Ott, et al, 2003, is cited, but is not reported in the reference list. In addition, the work of Phillips et al, constituting a massive study of personal exposure to RSP is ignored, as is the work of the TEAM study.

Page V-34 Table V-9

The "estimate" of RSP levels in homes (presumably smoking homes, although this is not called out) ranging from 300 – 5,500 $\mu g/m^3$ is simply unsupported by the scientific literature. The authors of the Report need to support this claim clearly. In addition, to state that such estimates represent "the best concentration estimates for each microenvironment" borders on the preposterous, and acts to destroy the credibility of this Report.

Page V-34

Exposure Estimation Scenarios

At first blush, it may appear that providing a variety of exposure scenarios for representative situations might be a useful exercise. However, the devil is in the details, and for these cases, the details of exposure scenarios described suggest that such analyses have little basis in reality. Two examples are illustrative.

Consider Scenario C1, the Children's Low Exposure Scenario. The only source of exposure that is calculated is for the child playing outdoors in an area that is adjacent to a neighboring business's smoking area. As a surrogate for the concentrations to which the child is exposed, the authors of the report use the mean level of the outdoor smoking area outside a business. It should be noted that a) the CARB outdoor analysis (Appendix C) has not yet been reported in the peer-reviewed literature, nor is there any evidence that it has been accepted for publication. A review of the details in Appendix C reveals that, inexplicably, the investigators used an unconventional method for collection of ETS nicotine (sampling at 15 L per minute). There is no data provided to indicate that the methodology (either sampling or analysis) is comparable in performance to the widely accepted ASTM method for airborne nicotine (ASTM, 2001) nor whether the sampling and analysis method used has been reported in the scientific, peer reviewed literature. From what I can determine, it has not. (It should be noted that in a review of Appendix C, that discusses the analysis of the ambient air nicotine samples, I was unable to find any reference to the use of an internal standard for the GC/MS analysis of nicotine. If this proves to be the case, and the analytical lab really did employ an inherently non-quantitative technique (mass spectrometry) in an attempt to provide quantitative data without the use of an internal standard, the value of all the analytical results are called into question. It may be likely that the study would have to be repeated with better laboratory practices.)

Additional examination of the sampling scenario provides no data as to the actual size of the smoking areas. However, we do know that one of the samplers was placed on the edge of the smoking zone and a second sampler placed in the center of the area. Mean concentrations for the center and edge of the smoking area were used as a surrogate for the concentration to which a child playing in an area adjacent to the smoking area would be exposed. This strains credibility, since it would seem that, given the likely distance of the child in its play area from the actual smoking area and the likely dispersion of the ETS, the best concentrations to use would have been the **background** concentrations determined from the outdoor measurements. The child is not going to play in the middle of the smoking area, yet these are the concentrations that are used. This kind of scenario description severely diminishes the utility of the approach.

A second example is simpler. Scenario T1 is the Business Traveler scenario. This scenario includes a non-smoking business traveler standing outside an airport for one hour in a designated outdoor smoking area. It is extremely difficult to imagine how such would occur, realistically. A five-minute exposure duration might have been more credible.

These two examples suggest that the authors of the Report were seeking to boost exposure levels in these scenarios by using unrealistic situations. The authors need to revisit each scenario, and use both realistic concentrations (for example, background nicotine concentrations for the child) and realistic durations. Without doing this, the examples provided have no useful value, and damage the overall credibility of the report. Given the quality of the existing scenario, the statement on Page V-34 that a statewide analysis exposure estimate would be "less informative" than the examples provided is simply not true.

Section F Biological Markers of Exposure to ETS

Summary comments and concerns are as follows:

1. In many places, the review of the scientific literature is incomplete. Key data presentations have been ignored.

2. Criticism, either direct or thinly veiled, is leveled at some but not all of the studies. This provides an unnecessarily advocative tone to the Report, which seriously diminishes its credibility. If the authors believe that an analysis of the strengths and limitations of studies are useful to the discussion, then such an analysis must be performed on all of the studies considered for discussion.

3. No analysis was performed on the only California-specific data set available for personal exposure to nicotine and salivary cotinine levels, despite the fact that such data has been publicly available for years.

4. There is discussion of biomarker levels in smoking mothers, but no effort is made to rationalize its connection with the topic of section: biomarkers and ETS exposure.

5. There are no substantive conclusions for this section with regard to the stated objective (page V-50) to examine "the utility of biomarkers to assess the extent of exposure to ETS." The "conclusion," that cotinine in body fluids can be used to distinguish smokers from ETS exposed individuals, is hardly a quantitative assessment, and ignores key scientific findings in the area. These are a) overall indicators of exposure (number of cigarettes observed to have been smoked near subjects, smoking/non-smoking home/workplace classification groupings, etc, show proportional increases in cotinine levels for increasing nicotine exposure when data from individuals is composited into larger groupings. (This may be due to dampening of individual differences in metabolism.); b) individual cotinine levels, while having statistically significant correlations with nicotine exposure, appear to have little *quantitative* predictive capability (in other words, one cannot use cotinine level to quantitatively predict an individual's exposure to within a factor of 2, or even 5); c) models based on metabolism of nicotine by smokers appear to be unable to quantitatively estimate the magnitude of inhaled dose of nicotine; and d) other biomarkers of tobacco specific constituents, such as tobacco specific nitrosamines, may ultimately be useful for qualitative or even semi-quantitative indicators of inhaled ETS dose. However, the analytical challenges of measuring extremely trace quantities of these markers in biological fluids are preclude their applicability to broad studies of ETS dose at this time.

Specific Comments:

Page V-54

The 16 Cities Study was not performed by LaKind et al. The 1999 manuscript is a further analysis of the data reported first (and conducted by) Jenkins et al, 1996.

If it is important to provide the reader with funding sponsorship or affiliation of authors, then full disclosure should be made for all authors cited: eg. Smith et al, 2005, well-recognized anti-smoking

advocates, reported ..... Frankly, if the data have been reported in the peer reviewed literature, sponsorship or the personal preferences of the authors should not be considered in the analysis. Period.

Also, Dietrich Hoffmann's name is incorrectly spelled at the bottom of the page.

Page V-55

The statement that the EPA had raised a multitude of concerns (unspecified) regarding the 16 Cities Study in some post hearing commentary in February of 1996, when the peer-reviewed manuscript was not even published until December 1996, suggests that the authors are bending over backward to appear as advocates, rather than dispassionate, unbiased assessors of the scientific data.

Also, it should be noted that the 16 Cities Study reported personal exposures, and the work described in Hammond et al, 1999 are ***area*** concentrations of ETS nicotine. As such, the two data sets are not comparable.

Finally, the statement is made that personal exposure nicotine concentrations reported by Phillips et al (1998) in Prague are lower than in comparable studies. The reference to comparable studies is unclear. Do the author's mean compared to Phillips' other studies (most of which have, inexplicably, not been even cited by the report). Do the author's mean lower than the US 16 Cities Study? Whatever studies that are considered truly comparable to the Phillips work (large number of subjects, careful segregation of exposure types, breathing zone personal monitoring) need to be specifically cited here.

V-58

"The .... validity of workplace nicotine levels has been challenged..." Which workplace nicotine levels? Those reported by Phillips for Prague? If the authors want to critique individual studies, then the criticism needs to be spelled out and it needs to be done for all studies that are included in the data analysis. My suspicion is that the authors are referring to a criticism of the 16 Cities Study (Jenkins et al, 1996) published many months prior to the publication of the peer-reviewed manuscript. To include such comments without specifying the criticism gives a tone of apparent bias to the entire Report.

Also, despite the fact that the data from the 16 Cities Study for Fresno (nicotine exposure and salivary cotinine levels that could have been analyzed) has been available for years (see the last page of Graves et al, 2000, or http://www.ornl.gov/sci/csd/Research_areas/ecms_rd_etsce_16cities.html), the authors of the Report did not analyze that data.

Finally, the analysis by LaKind et al (1999) of salivary cotinine levels from the 16 Cities Study shows median salivary cotinine levels for subjects only exposed in the workplace (Cell 3, Table V-15) of 0.347 ng/mL. When corrected for typical differences between saliva and serum cotinine levels, the levels reported by Pirkle et al (1996) for subjects exposed only in the workplace would be 0.40 ng/mL. To report a criticism of the 16 Cities Study by EPA regarding workplace nicotine levels, and then have the actual cotinine values reported by two independent groups be nearly indistinguishable makes not sense. This sort of biased data presentation jeopardizes the credibility of the Report, and calls other conclusions by the authors of the Report into question.

Page V-59

The original data analysis of salivary cotinine and nicotine exposure from the US 16 Cities Study (Jenkins and Counts, 1999b) is not even cited in the references for the chapter. Also, the presentation of the cotinine data from NHANES III, reported in Pirkle, (1996), even though it is segregated such that it

would be directly comparable to that reported by LaKind et al (1999) is missing from this analysis. In addition, the whole body of Phillips' work (eg, Phillips et al, 1998, etc) is not referenced or discussed in the Report. This one page affords several examples of inadequate literature review, reporting and analysis of the applicable scientific literature for this Report. It would be easy for the reader to draw the conclusion that if *these* key studies are not considered, *other* key investigations in other parts of the report have been ignored.

Page V-65

The authors need to clarify the relevance of maternal smoking biomarkers to the topic being discussed in the Report. Such is not evident on this page.

Chapter 6 Atmospheric Persistence

The discussion in Chapter 6 is interesting. A considerable about of data is presented to suggest that the lifetime of various components is, in some cases, is fairly short. However, there is little attempt to discuss the rationale of using outdoor air markers (such as the iso-alkanes or ante-isoalkanes) as long term markers for ETS in ambient air when many of the components of ETS have relatively short half lives outdoors. This apparent inconsistency needs to be addressed.

Page VI-1

The statement " .....Alternatively, as ETS ages, semi-volatile constituents of ETS, such as nicotine, may shift from particulate phase to the gaseous phase....." seems to be incongruent with the latest scientific evidence regarding the state of nicotine in ETS. Most nicotine in fact is in the vapor phase of ETS (mainly emanating from sidestream smoke) as the ETS begins to form. A much better example of the shift from particle phase to vapor phase would be neophytadiene or n-$C_{27}H_{56}$.

Page VI-2

The data reported in Table VI-1 presents a large range of atmospheric lifetimes for known constituents of ETS. The reported range is 5 minutes to 12 days. Given this data, and the likely reactivity of many of the other constituents of interest, it seems very hard to make a case that what we refer to as "environmental tobacco smoke" is likely to maintain much of its character after a few tens of minutes in the outdoor air. Given such, one would have expected for the Report to provide some rationale as to why it is reasonable to consider ETS wholistically as a toxic air contaminant. Such is missing from this report. Without a clear, strong justification as to why we should consider ETS as some sort of single entity, when it is clearly not such, it would seem that the pollution which results from ETS best be considered on a constituent by constituent basis. Many of the compounds of interest are already regulated under a variety of regulations. No compelling evidence is provided for the case that ETS survives as an entity and should be considered as such.

References Cited

American Society for Testing and Materials (2001), Standard D 5075 – 01 Standard Test Method for Nicotine and 3-Ethenylpyridine in Indoor Air

Panagiotis Georgiadis, Melpomeni Stoikidou, Jan Topinka, Stella Kaila, Maria Gioka, Klea Katsouyanni, Radim Sram, Soterios A. Kyrtopoulos (2001) "Personal exposures to PM 2.5 and polycyclic aromatic hydrocarbons and their relationship to environmental tobacco smoke at two locations in Greece," Journal of Exposure Analysis and Environmental Epidemiology 11, 169 - 183

Gevecker Graves, C.,Ginevan, M. E., Jenkins, R. A., Tardiff, R. G.. (2000). "Doses and lung burdens of environmental tobacco smoke constituents in nonsmoking workplaces." J Expo Anal Environ Epidemiol 10(4): 365-77.

Heavner, D. L., Morgan, W. T., & Ogden, M. W. (1996) Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. Environ. Int., 22, 159-183

Roger A. Jenkins, Ralph H. Ilgner, Bruce A. Tomkins, Douglas W. Peters, (2004) "Development and Application of Protocols for the Determination of Response of Real Time Particle Monitors to Common Indoor Aerosols," Journal of the Air & Waste Management Association, 54: 229 - 241

Jenkins, RA and Counts R.W., (1999) "Occupational Exposure to Environmental Tobacco Smoke: Results of Two Personal Exposure Studies" Environmental Health Perspectives 107 Suppl 2 341 – 348

Jenkins, R.A and Counts, R.W. (1999b),"Personal Exposure to Environmental Tobacco Smoke: Salivary Cotinine, Airborne Nicotine, and Non-smoker Misclassification", Journal of Exposure Analysis and Environmental Epidemiology, 9, 352 - 363

Jenkins, R.A., Guerin, M.R., and Tomkins, B.A., The Chemistry of Environmental Tobacco Smoke: Composition and Measurement, Second Edition, Lewis Publishers, Boca Raton, FL, 467 pp, (2000)

Roger A. Jenkins, Michael P. Maskarinec, Richard W. Counts, John E. Caton, Bruce A. Tomkins, and Ralph H. Ilgner "Environmental Tobacco Smoke (ETS) in an Unrestricted Smoking Workplace: Area and Personal Exposure Monitoring" Journal of Exposure Analysis and Environmental Epidemiology, 11: 369 - 380, 2001

Roger A. Jenkins, Andi Palausky, Richard W. Counts, Charles K. Bayne,Amy B. Dindal, and Michael R. Guerin, "Exposure to Environmental Tobacco Smoke in Sixteen Cities in the United States As Determined by Personal Breathing Zone Air Sampling," Journal of Exposure Analysis and Environmental Epidemiology, 6,(4) 473 - 502, (1996)

Leaderer, B. P. & Hammond, S. K. (1991) Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. Environ. Sci. Technol., 25, 770-777.

Maskarinec, M.P., Jenkins, R.A., Counts, R.W., and Dindal, A.B., "Determination of Exposure to Environmental Tobacco Smoke in Restaurant and Tavern Workers in One US City" Journal of Exposure Analysis and Environmental Epidemiology,10, 36 - 49, 2000

Phillips, K., Howard, D. A., Browne, D., & Lewsley, J. M. (1994) Assessment of personal exposures to environmental tobacco smoke in British nonsmokers. Environ. Int., 20, 693-712.
Phillips, K., Howard, D. A., Bentley, M. C., & Alvan, G. (1998) Assessment by personal monitoring of respirable suspended particles and environmental tobacco smoke exposure for non-smokers in Sydney, Australia. Indoor Built Environ., 7, 188-203.

Phillips, K., Howard, D. A., Bentley, M., & Alvan, G. (1998) Measured exposures by personal monitoring for respirable suspended particles and environmental tobacco smoke of housewives and office workers resident in Bremen, Germany. Int. Arch. Occup. Environ. Health, 71, 201-212.

Phillips, K., Bentley, M. C., Howard, D. A., & Alvan, G. (1998) Assessment of air quality in Paris by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. Environ. Int., 24, 05-425.

Phillips, K, Bentley, M. C., Howard, D., & Alvan, G. (1998) Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Kuala Lumpur using personal monitoring. J. Expo. Anal. Environ. Epidemiol., 8, 519-541.

Phillips, K., Howard, D. A., Bentley, M. C., & Alvan, G. (1998) Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Hong Kong using personal monitoring. Environ. Int., 24, 851-870.

Phillips, K., Bentley, M. C., Howard, D. A., Alvan, G., & Huici, A. (1997) Assessment of air quality in Barcelona by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. Environ. Int., 23, 173-196.

Phillips, K., Bentley, M., Howard, D., & Alvan, G. (1998) Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Prague using personal monitoring. Int. Arch. Occup. Environ. Health, 71, 379-390.

Phillips, K., Howard, D. A., Bentley, M. C., & Alvan, G. (1998) Assessment of environmental tobacco smoke and respirable suspended particle exposure of nonsmokers in Lisbon by personal monitoring. Environ. Int., 24, 301-324.

Phillips, K, Howard, D. A., & Bentley, M. C.. (1997) Assessment of air quality in Turin by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. Environ. Int., 23, 851-871.

Phillips, K., Howard, D. A., & Bentley, M. C. (1998) Exposure to tobacco smoke in Sydney, Kuala Lumpur, European, and Chinese cities. Proceedings of the 14th International Clean Air & Environment Conference, Melbourne, Australia, Oct. 1998, pp. 347-352

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Phillips, K., Bentley, M. C., Howard, D. A., & Alvan, G. (1996) Assessment of air quality in Stockholm by personal monitoring of nonsmokers for respirable suspended particles and environmental tobacco smoke. Scan. J. Work. Environ. Health, 22, 1-24.

Phillips, K., Howard, D. A., Bentley, M., & Alvan, G. (1999) Assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Basel by personal monitoring. Atmos. Env., 33, 1889-1904.

Phillips, K., Howard, D. A., Bentley, M. C., and Alvan, G. (1998). Environmental tobacco smoke and respirable suspended particle exposures for non-smokers in Beijing. Indoor Built Environ., 7, 254–269.

Sterling E.M., Collett C. W., Ross, J. A. (1996) Assessment of non-smokers' exposure to environmental tobacco smoke using personal-exposure and fixed location monitoring. Indoor Built Environ., 5, 112–125.

Trout, D., Decker, J., Mueller, C., Bernert, J. T., and Pirkle, J. (1998) Exposure of casino employees to environmental tobacco smoke, J. Occup. Environ. Med., 40(3) 270–276.

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March 1, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street / P.O. Box 2815
Sacramento, California 95812

RE: Comments on Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, Draft Report, December 2003

Dear Ms. Brooks,

Thank you for providing an opportunity to comment on the draft staff report on Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. My experience on the health effects of air contaminants includes 30 years of study of air pollution in California as a director of the Air Pollution Health Effects Laboratory in the College of Medicine at the University of California, Irvine, and performance as a principal investigator on numerous relevant grants and contracts funded by state (ARB, DHS, TRDRP and TSRTP), federal (NHLBI, CDC, EPA and NIEHS) and private (EPRI, SCE, and NIPERA) agencies. In that regard, I have consistently seen that a critical factor in human health effects is the dose of contaminant actually delivered to target tissues in the body.

My main concern with the draft report is its failure to clearly state that the doses of environmental tobacco smoke (ETS) that are experienced outdoors by nonsmokers in California are very small, and thus extremely unlikely to lead to any significant adverse health effects. The associations between ETS and adverse health outcomes are related to indoor/in vehicle exposures, which are very high in relation to outdoor exposures of nonsmokers. Thus, the adverse effects described in the draft report are not relevant to a consideration of identifying outdoor ETS as a potential Toxic Air Contamint (TAC).

Should the state entertain listing indoor ETS as a TAC, another issue should be addressed. An area of current research emphasis is that of the influence of tobacco smoking on levels of aggression. Frankly, existing human studies are somewhat contradictory, and animal studies have only begun to look for possible mechanisms. For in-home smoking, there may be risk tradeoffs between the direct health risks of ETS and the risks of increased violence.

It is important that public health professionals and the public focus on risks that are not trivial, because the resources available are limited. Spending time and money on negligible exposures diverts attention from more serious public health problems. Also, where there are risk

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tradeoffs from regulations, those tradeoffs must be clearly identified and objectively assessed. In summary, the draft report appears to magnify the potential effects of a negligible exposure to the extent that it is misleading.

Again, I appreciate the opportunity to provide this brief comment.

Sincerely,

Robert Phalen

Robert F. Phalen, Ph.D.
Professor and
Director of the Air Pollution Health Effects Laboratory

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March 03, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
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Dear Ms. Brooks:

I would like to respond to your invitation for written comments concerning your recent report, "Proposed Identification of Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant, November 2003. I specifically would like to comment on the section that deals with the risk assessment of ETS and breast cancer.

I am a Professor of Pathology at UCLA, a breast cancer researcher and practicing breast pathologist and I am very much interested in studying the etiologies of human breast cancer and defining the molecular mechanisms behind this very important disease of women.

The current draft of the present report of the Air Resources Board starts out by saying that the evidence linking ETS and breast cancer has considerably strengthened since the 1997 Report was published. The 1997 Report entitled, "Health Effects of Exposure to Environmental Tobacco Smoke", considered the relationship of ETS with breast cancer inconclusive and made the statement that this relationship must be interpreted cautiously (1). The current draft of the present report states "In comparison to studies reviewed in the previous OEHHA report (Cal/EPA, 1997) current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk.... Overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer ...."(2).

Let's begin with the biomarker studies. The biomarker studies consist of the demonstration that polycyclic aromatic hydrocarbons (PAH) were found in breast tissue of subjects and higher levels were found in their tumors. The levels of PAH adducts were not observed however to be associated with current active or passive smoking exposure. If one examines all the tissues of the body, the highest levels of PAH-adducts are actually found in heart tissue (3), a tissue that does not give rise to cancer and a tissue that is therefore resistant to the effects of smoking-related carcinogens. So the absolute or relative levels of PAH-adducts in of themselves do not constitute a meaningful biomarker. If evidence of molecular damage from the adducts such as mutations could be shown in breast tissue such as the characteristic G→T transversion of PAH or if, phenomenon related to genomic instability, such as loss of heterozygosity (LOH) or microsatellite instability as has been shown to be present in bronchial tissues of smokers (4,5) had been demonstrated in breast tumors of people exposed to ETS that in fact would be evidence of a biomarker. PAH-adducts alone for the reasons cited are not enough. Therefore the weight of biomarker evidence does not support a causal association between ETS and human breast cancer.

Animal models purporting an association of ETS and breast cancer are also lacking. Most animal models of breast cancer are mouse models and are related to either the mouse mammary tumor virus (MMTV) or the genetically engineered mouse (GEM) where certain oncogenes such as *myc* and *neu* are overexpressed (6). There are only a few models of PAH-induced mammary tumors, the most common example of which is dimethylbenzanthracene (DMBA). However carcinogen-induced mammary tumors including DMBA are not metastatic (6). Hence the scarcity and overall relevance of these murine models to ETS and human breast cancer is questionable. Certainly the weight of the evidence provided by these animal studies is not sufficient to show a causal association between ETS in breast cancer.

Past epidemiological studies really have provided the weight of the evidence suggesting a causal association between ETS and human breast cancer but the current draft of the present report either ignores mentioning or does not give the appropriate weight to recent studies which refute this association. Before I cite and discuss these recent studies, I would like to point out some of the shortcomings of many of the previous studies which the current draft cites.

Firstly, it is important to emphasize that human breast cancer is a heterogeneous disease consisting of both life-threatening variants, breast-threatening variants and innocuous variants which are incidental findings. Obviously the first of these disease types is of more concern to the general public than the last of these types. The vast majority of the epidemiological studies cited in the current draft lumps all of breast cancer together. The few studies which look at breast cancer mortality (the first of these disease types) find no association with ETS.

Secondly, it is important to emphasize that the data demonstrating a relationship between ETS and human breast cancer must do so in a biologically plausible manner. If there indeed is an association between ETS and human breast cancer, there must be an association between mainstream smoking and breast cancer and the latter association must be stronger. That is so because the carcinogenic exposure is greater with mainstream smoke. Yet none of the epidemiological studies which the current draft cites show a greater association with mainstream smoking (7-11). An argument advanced to reconcile this disparity is that the control group may have consisted, in part, of people exposed to ETS and thus had a higher rate of breast cancer than would have been expected (2). Differences in breast cancer incidence between this control group and the smoking group would have therefore been minimized. However even this argument would fail to explain why the rate of breast cancer was not higher in the smoking group. The smoking group would consist of subjects exposed to mainstream smoke and hence to the maximal levels of carcinogens. The control group even if it was composed of never smokers and subjects exposed to ETS would still have an overall reduced level of carcinogen exposure and therefore a reduced incidence of breast cancer compared to the mainstream smoking group. But that was not what was observed. Smokers did not have a higher incidence of breast cancer than ETS exposed subjects.

Thirdly, none of the epidemiological studies mentioned in the current draft propose a credible biological mechanism to explain the observations of the study on the relationship of ETS to breast cancer. For example, there is no demonstration that people exposed to ETS have a higher level of cotinine or a higher level of DNA adducts or more mutations in their breast tissue than controls.

Fourthly, the present draft cites many studies with very small numbers of patients (8,12). When dealing with relative risks or odds ratios in the 1.x range, large numbers of subjects are essential for conclusions of statistical significance.

Fifthly, the present draft cites studies which are mainly retrospective and not prospective in nature (10,11,12). Retrospective studies are inherently much weaker than prospective studies. Only a single prospective study (13) is cited by the present draft. This study by Jee *et* al. showed an increased incidence of breast cancer in spouses exposed to ETS from their husbands' smoking but whether this association rose to statistical significance can be raised.

Sixthly, some studies cited in the present draft, *eg.* Lash *et* al. (11), published in 1999 and showing an association between ETS and breast cancer were refuted in subsequent studies by the same authors, *eg.* Lash *et* al. (14) in 2002.

Seventhly, the studies linking genetic polymorphisms with breast cancer risk and ETS are inconclusive or show no association between ETS and breast cancer irrespective of polymorphisms (15,16).

Finally and most importantly the present draft fails to cite or properly acknowledge the importance of recently emerging powerful and compelling prospective studies published since 2000 all of which have showed no association between ETS and breast cancer (17-20). These prospective studies have the power of large number of subjects enrolled and have been published in peer reviewed journals of the highest impact factors. In the first study, the Reynolds study (2004) (17), which was just recently published, it was found that 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. Furthermore, breast cancer risks among never smokers reporting household passive smoking exposure were not greater than those among never smokers. Their study provided evidence that active smoking but not passive smoking exposure may play a role in breast cancer etiology. In the second study, the Wartenberg study (2000) (18), the authors concluded that, "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". The third study, Nishino *et* al. (19), and the fourth study, Egan *et* al. (20) are also both prospective studies showing no relationship between ETS and breast cancer.

Because of all these cited reasons, I am concerned that the conclusion of the present draft concerning the relationship between ETS and breast cancer simply is not supported by the data and that the most

recent and most powerful studies have not strengthened the association between ETS and breast cancer but actually weakened it. It is important in considering the totality of evidence not simply to add up the studies for and against an observation but to rank order the studies. All studies in science are not created or conducted equally ! For example studies with large numbers of subjects, all other things being equal, are superior to studies with a small number of subjects. Prospective studies, all other things being equal, are superior to retrospective studies. Studies published in highly regarded peer reviewed journals with high impact factors (the average number of times their articles are quoted by other studies), all other things being equal, are superior to studies published in less known journals with low impact factors. Studies which are peer-reviewed are superior to studies which are not peer reviewed such as letters to the editor, etc.

Simply stated, the studies which show no association of ETS with breast cancer are prospective, comprised of large numbers of subjects, recent and published in journals of the highest impact factors (17-20). The studies which show a relationship of ETS with breast cancer are retrospective, comprised of a small number of subjects, older and published in low impact journals (8,10,12) or published not as peer reviewed articles at all but rather as letters to the editor (21,22).

It is also pertinent to point out to the Air Resources Board that another environmental protection agency, the International Agency for Research on Cancer, whose overall mission is similar to that of the California Environmental Protection Agency and who, in the past, has warned the public about the risks of smoking and the dangers of ETS issued the following report in 2002: "Concerns that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking is unjustified by the evidence" (23). Their report further goes on to state: "The collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent. Although 4 of the 10 case control studies found statistically significant increased risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal association between involuntary exposure to tobacco smoke and breast cancer in never smokers. The lack of a positive dose response also argues against a causal interpretation of the findings. Finally the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking."

Certainly both mainstream smoking and exposure to ETS are not good things for our society to have to deal with and it would be best if these practices could be eliminated. But it is important to accurately evaluate which diseases are and which diseases are not associated with either exposure.

One may ask what is the danger of overstating a potential risk factor in the etiology of any disease. The danger is that it will detract from finding the real culprit. In the case of breast cancer, we really do not know what the cause of the disease is and we need to find out. We need also to identify the major risk factors (both environmental and genetic) to explain sporadic breast cancer, by far the most common type of breast cancer.

As presently stated, the current working draft of the Air Resources Board claims that overall, the weight of the evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between ETS in breast cancer. I fear that this current draft has not given enough weight to the newer emerging prospective studies that have been published in outstanding peer review journals of high impact factors that show no association of ETS with breast cancer and has ignored the recent 2002 report of the International Agency for Reseach on Cancer that also concludes that there is no such association. These studies should be acknowledged and the report's conclusions about the association of ETS and human breast cancer should at least be modified in the face of this new emerging data.

I would hope that the arguments advanced in this letter would cause the Air Resources Board to at least rethink its position on this matter.

I wish to disclose to the Air Resources Board that I was contacted by R.J Reynolds and asked to review the current draft of the report of Chapter 7, conduct a review of the medical and scientific literature on breast cancer and ETS and prepare my written comments. I was compensated for the time spent on these endeavors.

Respectively submitted,

Sanford H. Barsky, M.D.
Professor of Pathology

References

1. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Health Effects of Exposure to Environmental Tobacco Smoke, Final Report, September, 1997.
2. California Environmental Protection Agency, Air Resources Board, Office of Environmental Health Hazard Assessment, Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant [Draft], December 2003.
3. Randerath E, Miller RH, Mittai D, Avitts TA, Dunsford HA, Randerath K. Covalent DNA damage in tissues of cigarette smokers as determined by ^{32}P-postlabeling assay. *J Natl Cancer Inst* 81: 341-347, 1989.
4. Wistuba II, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, Samet JM, Srivastava S, Minna JD, Gazdar AF. Molecular damage in the bronchial epithelium of current and former smokers. *J Natl Cancer Inst* 89: 1366-1373, 1997.
5. Mao L, Lee JS, Kurie JM, Fan YH, Lippman SM, Lee JJ, Ro JY, Broxson A, Yu R, Morice RC, Kemp BL, Khuri FR, Walsh GL, Hittelman WN, Hong WK. Clonal genetic alterations in the lungs of current and former smokers. *J Natl Cancer Inst* 89: 857-862, 1997.
6. Advances in human breast cancer research: Preclinical models. The 24th Congress of the International Association for Breast Cancer Research. Sacramento, CA 2003.
7. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol* 156: 616-626, 2002.
8. Morabia A, Bernstein M, Heritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol* 143: 918-928, 1996.
9. Smith SJ, Deacon JM, Chilvers CED. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br J Cancer* 70: 112-119, 1994.
10. Johnson KC, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994-1997. *Cancer Causes and Control* 11: 211-221, 2000.
11. Lash TL, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* 149: 5-12, 1999.
12. Sandler DR, Everson RB Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 121: 37-48, 1985.
13. Jee SH, Ohrr H, Kim HS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *International J Epidemiol* 28: 824-828, 1999.

14. Lash TL, Aschengrau A. A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat* 75: 181-184, 2002.
15. Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao SY, Gim JSY, Ma HL, Butler J, Anton-Culver H. Breast cancer passive and active Cigarette smoking and N-acetyltransferase 2 genotype. *Pharmacogenetics* 10: 461-469, 2000.
16. Millikan RC, Pittman GS, Newman B, Tse CKJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA. Cigarette smoking, N-acetyltransferase 1 and 2 and breast cancer risk. *Cancer Epidemiology Biomarkers and Prevention* 7: 371-378, 1998.
17. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A. Active smoking household passive smoking and breast cancer: Evidence from the California Teachers study. *J Natl Cancer Inst* 96: 29-37, 2004
18. Wartenberg D, Calle EE, Thun MJ, Heath CW, Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* 92: 1666-1673, 2000.
19. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes and Control* 12: 797-802, 2001.
20. Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA. Active and passive smoking in breast cancer: Prospective results from the nurses' health study. *Epidemiology* 13: 138-145, 2002.
21. Wells AJ. Breast cancer, cigarette smoking and passive smoking. *Am J Epidemiol*133: 208-210, 1991.
22. Wells AJ. Breast cancer, cigarette smoking and passive smoking. *Am J Epidemiol* 147: 991-992, 1998.
23. Press Release, IARC Monographs Programme declares second-hand smoke carcinogenic to humans. International Agency for Research on Cancer, 2002.

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Ms. Janette Brooks
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California Air Resources Board
Attention: Environmental Tobacco Smoke
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February 16, 2004

DEPARTMENT OF
PUBLIC HEALTH

Dear Ms. Brooks,

We are responding to your request for comments on the draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, November 2003. This draft is an excellent extension of the initial California EPA report, "Health Effects of Exposure to Environmental Tobacco Smoke" (1999). We would like to focus our comments on one aspect of the draft report: the association between ETS and breast cancer.

We have been concerned for several years regarding the failure of national organizations and agencies to include in public statements, special reports, practice guidelines and general education for health professionals and the public, the growing body of theoretical, basic, laboratory, animal, applied, and epidemiological data regarding the relationship between tobacco smoking and exposure to ETS and the risk of breast cancer. One of the authors (S Jay) outlined these concerns in CA A Cancer Journal for Clinicians: "Smoking as a Risk Factor for Breast Cancer in Women" 1998;48(3):190-191.

We believe that one of the reasons for this delayed response of regulatory agencies and professional organizations has been the publication of a few reports that purport to show no adverse effect of ETS exposure. We believe this finding is in part a result of the failure of researchers, until very recently, to control for exposure to ETS in both control and experimental groups in prospective population-based studies. A previous publication (Jay SJ. "Tobacco Blindness." Tobacco Control 1997;6:226-27) reviewed this serious methodological error in the design of most studies of clinical disease outcomes and "smoking" status. Of course, failing to control for ETS exposure will negate or minimize any differences in clinical research endpoints where the effects of "smoking" vs. "non-smoking" are being studied. In addition, studies of the relationship between ETS and disease outcomes, including breast cancer, have routinely failed to carefully control for ETS exposure over the duration of prospective studies. Quantitative measurements of exposure over time are rarely reported. For example, three recent studies that failed to show evidence of an association between ETS exposure and breast cancer risk, reported very limited data regarding ETS

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exposure (Egan et al., 2002; Jee et al., 1999; and Wartenberg et al., 2000). In the majority of studies that have used referent groups that were unexposed to ETS, risk estimates for breast cancer range from about 1.5 to 2.5. We recognize that other potentially confounding factors have not been routinely controlled for in many studies, e.g., menopause status, childhood exposure and the like. While the causal association between ETS in breast cancer appears to be greater for pre-menopausal breast cancer, we see no evidence from either earlier studies or more recent well controlled studies that would negate the conclusion that ETS is causally associated with breast cancer.

When these data are viewed in the context of the Bradford-Hill criteria for plausibility of a hypothesized causal relationship between tobacco smoking and exposure to ETS to breast cancer, we strongly believe that your conclusion (Table 7.0A ETS and Cancer: Comparison of OEHHA (1997) and Update) that current evidence of a causal association between ETS exposure and breast cancer is "conclusive" is warranted.

Thank you for considering our comments.

Sincerely Yours,

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March 29, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street, P.O. Box 2815
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Comments of the American Lung Association and the American Lung Association of California Concerning the Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant by the California Air Resources Board

The American Lung Association is pleased to have the opportunity to comment on the draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, November 2003." First, we would like to applaud the California Air Resources Board (CARB) and the Office of Environmental Health Hazard Assessment (OEHHA) for their leadership and significant contributions to the scientific evidence regarding the detrimental health effects and harms of environmental tobacco smoke (ETS). This 2003 report builds on the scientific evidence outlined in the 1997 report, by updating the scientific understanding of the exposure and health impacts significantly. As a leading public health organization, the American Lung Association appreciates the volume of data that was collected and synthesized for the draft report.

A Toxic Air Contaminant is defined in Health and Safety Code section 39655 as: "an air pollutant which may cause or contribute to an increase in mortality, in serious illness, or which may pose a present or potential hazard to human health." The American Lung Association believes that based on the fact that there are more than 4000 chemicals in ETS, including 69 that are carcinogenic, the case is clear that ETS should be identified as a toxic air contaminant under California law.

While ETS is clearly linked to number of other health problems, the American Lung Association's comments will be limited to the impacts on respiratory health only. For over twenty years, the evidence has been building on the causal associations between environmental tobacco smoke and lung cancer and other respiratory effects. In 1982, the U.S. Surgeon General first raised concerns that toxins present in tobacco smoke might be causing lung cancer not only in those who smoke, but also in those who involuntarily breathe secondhand smoke. It stated, "although the currently available evidence is not sufficient to conclude that passive smoking causes lung cancer in nonsmokers, the evidence does raise concerns about a possible serious public health problem."

Scientific research into this concern led the U.S. Surgeon General to report compelling evidence in 1986, which was confirmed by research by the National Research Council and U.S. Environmental Protection Agency, concluding that ETS exposure does cause lung cancer and other respiratory outcomes. Much of the research reported in the Draft Report on ETS exposure and lung cancer amplifies and confirms what has been known and accepted for years. We commend the staff on the thorough compilation of new work that continues to strengthen this link.

We would encourage the Science Advisory Panel to examine the methodology behind the attributed lung cancer deaths in your two reports. Currently the CDC and the 1997 Cal EPA report state that 3000 lung cancer deaths are attributed to ETS nationwide, which first appeared in U.S. EPA's 1993 analysis. We understand that this number may be outdated and underestimate the risk, but the attributable incidence and death estimates in the Draft Report are considerably higher. We understand that typographical and calculation errors on ES-11 and 7-76 that address this issue will be revised before the Science Advisory Panel reviews the next draft. More discussion of the methodology to reach both the California and national estimates is needed in the final report to justify this disparity and allow for comment. In order to be consistent, we would suggest using lung cancer deaths versus incidence as the point of comparison in Executive Summary Table ES2.

Another important topic reviewed in the Cal EPA report was the association of ETS with asthma exacerbations and induction. The American Lung Association is very interested in the scientific evidence that demonstrates linkages to asthma exacerbation, increases in asthma symptoms and induction of asthma from exposure to environmental tobacco smoke. We believe that the science is conclusive that ETS is a risk factor in the exacerbation of asthma in both children and adults. However, our review of the data in the Draft Report lead us to believe that the link to asthma induction in adults requires further scientific study to merit conclusive findings at this time. We encourage the Scientific Advisory Panel's investigation and comments on the staff report's recommendation to move from suggestive in the 1997 report to conclusive in this draft report regarding asthma induction in adults.

The issue of asthma induction in children is more complex. There is no doubt that higher rates of asthma exist in children of smoking parents. Prenatal exposure from a smoking mother does appear to alter lung growth and development *in utero* as the inhaled tobacco crosses the placenta. This would suggest a causal relationship between prenatal maternal smoking and asthma induction in children. Many of the studies in the Draft Report do not seem to distinguish between pre- and postnatal exposure. While the Lung Association supports the conclusive link of asthma induction in children, we would welcome a more robust examination of data that differentiates between pre- and postnatal exposure. It is very difficult to prove causal damage and the research is not as clear as to whether postnatal ETS exposure triggers an attack in a child who is predisposed to asthma or induces the first asthma attack of an existing condition. (Given the suggestive link between paternal smoking preconception and childhood cancers, this might also be another area of research to pursue in relation to childhood asthma induction in non-smoking mothers as well.)

It is becoming increasingly clear that environmental tobacco smoke is a serious toxic air contaminant, affecting the health of millions of Americans. We must continue to respond to the science with aggressive policy and legislation in order to lessen the impact of this deadly substance. We thank the State of California for expending the resources to update the scientific research associated with Environmental Tobacco Smoke and move that it finalize the report as a first step in strengthening protections from ETS.

If you would like to further discuss our comments, please contact Susan Rappaport at (212) 315-8791 or srappaport@lungusa.org or Paul Knepprath, at (916) 442-4446 or pknepprath@alac.org.

Sincerely,

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March 4, 2004

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street / P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Brooks:

Thank you for providing the California Department of Education (CDE) the opportunity to comment on the California Air Resources Board's draft report "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, December 2003." This document clearly shows the many causal links between environmental tobacco smoke (ETS) and health issues. Some of these issues are currently addressed in California's public schools as a result of Proposition 99, The Tobacco Tax Initiative.

With the passage of Proposition 99 in 1988, California public school districts have been required to implement tobacco-free school policies as a condition of receiving funds for tobacco-use prevention education (TUPE) and intervention programs in schools. This policy prohibits the use of tobacco products by students, staff, and visitors, at any time, in district-owned or leased buildings, on district property, and in district vehicles. As a result of this policy, approximately 95 percent of all California public schools have effectively eliminated ETS on district property. Schools are also required to present tobacco-use prevention lessons that include a discussion of ETS and its effects on the human body.

In addition, districts receiving TUPE funds are required to provide individualized counseling and advocacy services to all pregnant minors and minor parents regarding perinatal and postnatal tobacco use. The release of studies, including those cited in your report, are making school nurses and other school staff aware of the relationship between ETS and its adverse effects on the fetus, newborn, and older children.

I commend you and your staff for the thorough and unbiased examination of the many studies that have been conducted regarding ETS risks. The approval of this report will provide further corroboration of the need for existing and proposed policies that protect children and adults from the health risks associated with exposure to ETS. The health of children in particular has a great impact on their success in school as they cannot learn if they are home ill or not at their best in the classroom.

If you have any questions, please contact John Lagomarsino of the Safe and Healthy Kids Program Office, 916-323-1540.

Sincerely,

Wade S. Brynelson

WADE S. BRYNELSON
Assistant Superintendent
Learning Support and Partnerships Division

WB:jl

CAMPAIGN for TOBACCO-FREE KIDS

March 29, 2004

Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attn: Environmental Tobacco Smoke
1001 I Street/P.O. Box 2815
Sacramento, California 95812

Dear Ms. Brooks:

On behalf of the Campaign for Tobacco Free Kids, I am submitting comments in response to the December 2003 draft report issued by your agency entitled, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant."

First of all, the California Environmental Protection Agency (CalEPA) is to be commended for its comprehensive review of the scientific literature on environmental tobacco smoke (ETS), also known as secondhand smoke. This update of your agency's previous report (issued in 1997) on the same subject adds valuable, new information to the extensive clinical and experimental evidence that continues to accumulate regarding the risks of exposure to secondhand smoke and its relationship to various types of cancer, heart and lung disease, and other diseases in both children and adults.

The comprehensive and objective nature of the 1997 CalEPA report has enabled organizations like the Campaign to advocate for greater restrictions on exposure to secondhand smoke. The evidence from your 1997 report has been and continues to be central to our efforts to educate the public and key decision-makers about the need to limit public and workplace exposure to secondhand smoke. This prior work of your agency has given significant scientific credibility to our efforts to adopt smokefree workplace laws throughout the country. There is rarely a campaign to pass these laws today that does not include some of the basic information and statistics included in your 1997 report.

In addition, the long-term public health impact of your 1997 report is nothing short of remarkable. Since your 1997 report was issued, we have seen a fundamental shift in how the public views secondhand smoke and, as a result, we now have statewide, smokefree laws in not just California but in New York, Delaware, Connecticut, Maine, Idaho, and Florida. Several others states are actively considering such laws (including Massachusetts, Rhode Island, Washington, DC, and Georgia), and dozens of local communities have passed them.

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Your long-awaited update of the 1997 report will play a critical role in our efforts to protect everyone's right to breathe clean air free from the hazards associated with exposure to secondhand smoke. In addition, we are pleased to know (assuming your agency recommends that ETS be classified as a toxic air contaminant or TAC), that the final version of the report will be subject to an independent, external review by CalEPA's Scientific Advisory Board before moving forward with the final stages of the TAC regulatory process. This additional, independent process will enhance the credibility and value of this report as an important and new public health tool in the ongoing efforts to limit exposure to secondhand smoke in California and nationwide.

Thank you for the opportunity to comment on the draft report. We look forward to seeing the final version of the report and using it as part of our continued efforts to educate the public and to work toward passage of laws that protect everyone from the harms associated with exposure to secondhand smoke.

Sincerely,

William V. Corr
Executive Director