

III.

Comment Letters Received on the Draft ETS Report on Environmental Tobacco Smoke

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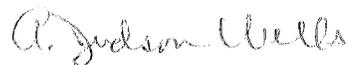
February 10, 2004

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, PhD

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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 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.

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 HealthWashington, DC., Appendix B. Reference 1992a 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 (Wartenberg) 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, et al., and Wartenberg, 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 there 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

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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.

Alyonik Hrushow, MPH
Tobacco Free Project Director



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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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Sacramento, California 95812

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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California Air Resources Board
March 25, 2004
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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*

Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
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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 Angeles 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 µm) 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/m³. 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/m³ 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/m³ and one million people exposed to an average cadmium concentration of 1.8 to 5.6 ng/m³.
- 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 PM₁₀ concentrations were 1.8 ug/m³ for 2000 and 1.7 ug/m³ 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

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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

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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,

A handwritten signature in black ink, appearing to read "B. McGinn", with a stylized flourish at the end.

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 FEV₁. 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 (≥ 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 (\geq 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 FEV₁/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.

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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/ confounders 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 exposure / 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 Diego 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 Diego 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 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, 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 Engineering'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". 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



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February 23, 2004

Janette Brooks
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California Air Resources Board
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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.

Janette Brooks
February 23, 2004
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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,

A handwritten signature in black ink, appearing to read "Dennis Eckhart", with a long horizontal flourish extending to the right.

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,

A handwritten signature in black ink, appearing to read "Diane J. Fink".

Diane J. Fink, MD
Chief Mission Delivery Officer

State Government Relations Office
1201 K Street, Suite 730 Sacramento, CA 95814
t) (916) 448-0500 f) (916) 447-6931

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A DAY IN THE LIFE
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2003 Annual Report
to the People of
California on Progress
in Cancer Control



Memorandum

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.



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**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

Janette Brooks, Chief

March 29, 2004

Page 2

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.

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).

Janette Brooks, Chief

March 29, 2004

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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

Janette Brooks, Chief

March 29, 2004

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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

James Repace, MSc.
Visiting Assistant Clinical Professor
Tufts University School of Medicine
and
Repace Associates, Inc.
101 Felicia Lane, Bowie, MD 20720
www.repace.com

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 Analytix; 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., $N = \sim 28$ 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

Total PPAH vs time, Feb 22, 2004, Summit Cruiseship Stateroom 2169
 Female Smoker, Marlboro Lights 100s, smoked for 6.7 min,
 air exchange rate $\phi = 6.63 \text{ h}^{-1}$. JL Repace using PAS2000CE

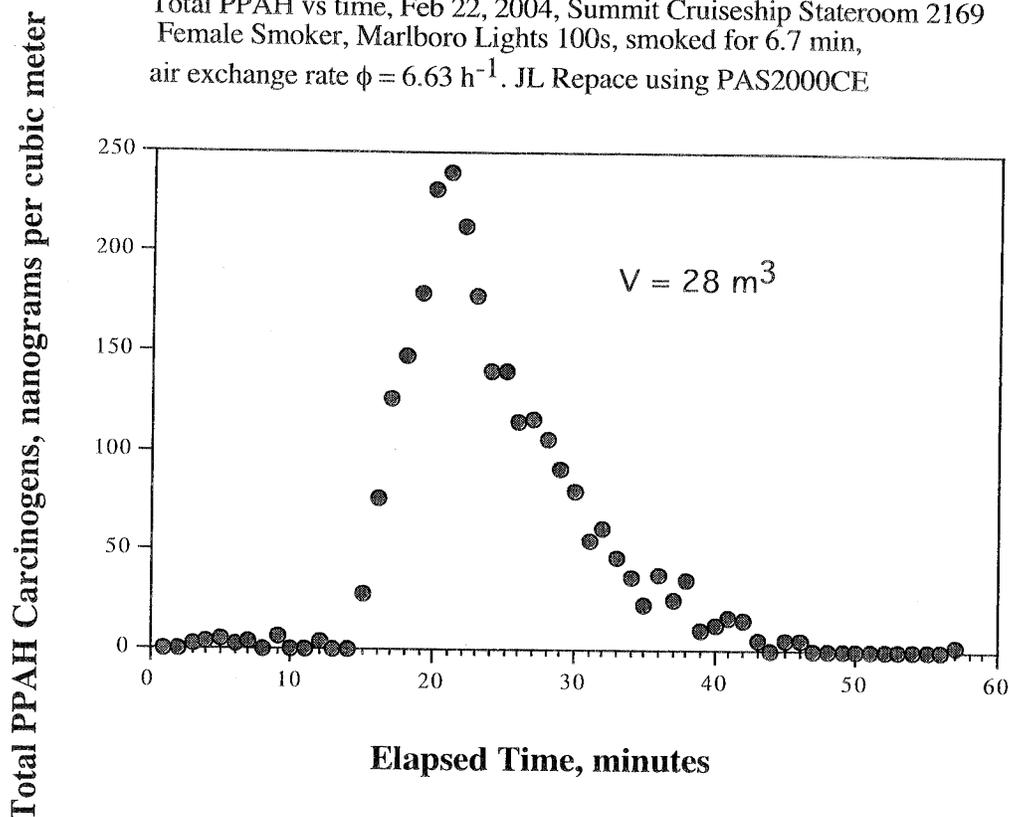


Figure 1. PPAH emissions before, during, and after a Marlboro Cigarette was smoked by a human smoker for 6.7 minutes in an inside stateroom on a cruise ship, consuming 0.55 g of tobacco.

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 $(0.983 - 0.258) = 0.725 \text{ g}$. 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 ($t_s = 6.7 \text{ min}$) is $X_{\text{max}} = 298 \text{ ng/m}^3$. The growth curve is given by the equation:

$$X_{\text{max}}(t_s) = (g_c/\omega)\{1 - e^{-(t/t_s)}\} \text{ (Equation 1),}$$

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, $\omega = 185.64 m^3/h$; $g_c = 1.763 \mu g$ PPAH/min, and the mass emissions of PPAH from the Marlboro Lite 100 cigarette smoked by a human smoker are:

$$G = g_c t_s = (\omega X_{max} t_s) / \{1 - e^{-(t_s/\tau)}\} = 21.22 \mu g/g.$$

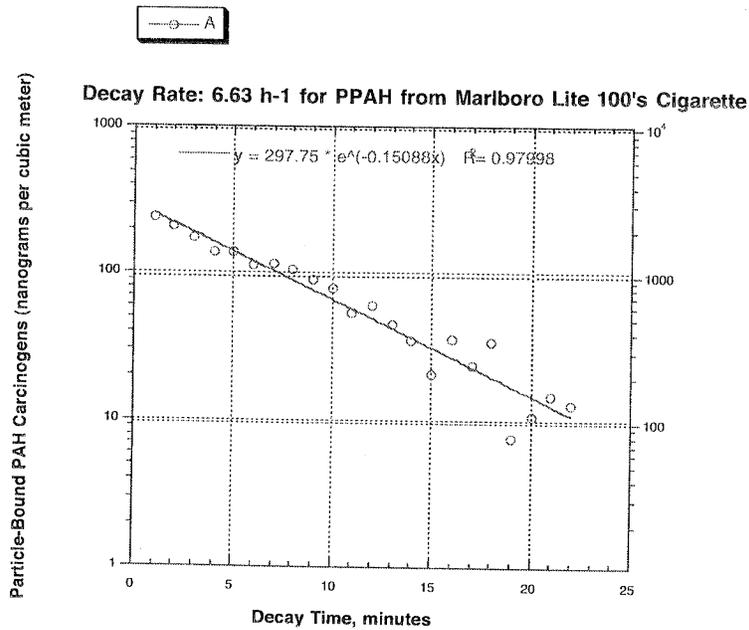


Figure 2. Semi-log plot of PPAH decay vs time for Figure 1, Marlboro Lite 100 Cigarette in a cruise ship stateroom. Background-subtracted decay curve $N = 22$ min.

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 $G_c = (21.22 \mu\text{g/g})(0.7\text{g}) = 14.85 \mu\text{g}$ 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 $(21.22 \mu\text{g/g})(0.7 \text{ g/cigarette})(25.4 \times 10^9 \text{ cigarettes}) = 377$ 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/m³) 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

^aOutlier removed: probably due to smoking on adjacent balcony; NR = not recorded

Table 2. Indoor/outdoor PPAH levels in ng/m³ 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

^aOutliers 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/m³ ave.) and one in the late evening (14.6 ng/m³); all data were combined and averaged (10.7 ng/m³) 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/m³. This is comparable to both the outdoor Deck 10 (8.9 ng/m³) and Deck 11 (11.12 ng/m³) Bars and the Cigar Bar (9.95 ng/m³) concentrations and the outdoor smoking (8.6 ng/m³) 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	<i>This Experiment</i>

*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/m³ (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/m³, in the presence of smoking, and averaging about 5 ng/m³ 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 1/6th 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.**

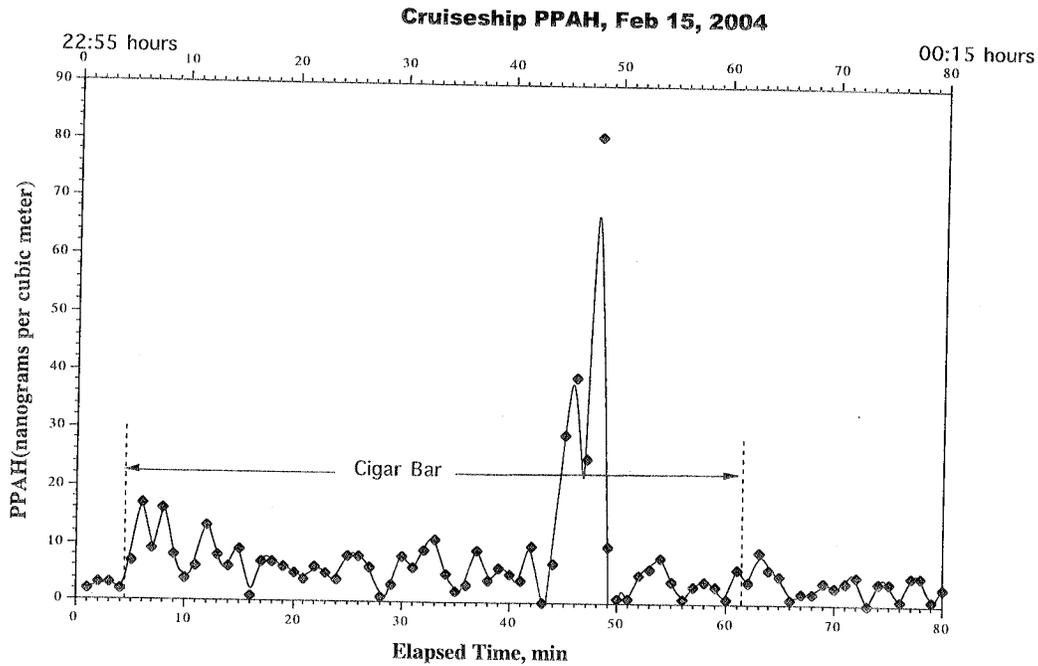


Figure 3. PPAH vs. time data. The clocktime recorded by the PAS2000CE monitor is converted into elapsed time for plotting purposes. The period shown is before, during, and after the Feb. 15 visit to the outdoor cigar bar during breezy conditions as described in Table 1. The large peak between 43 and 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.

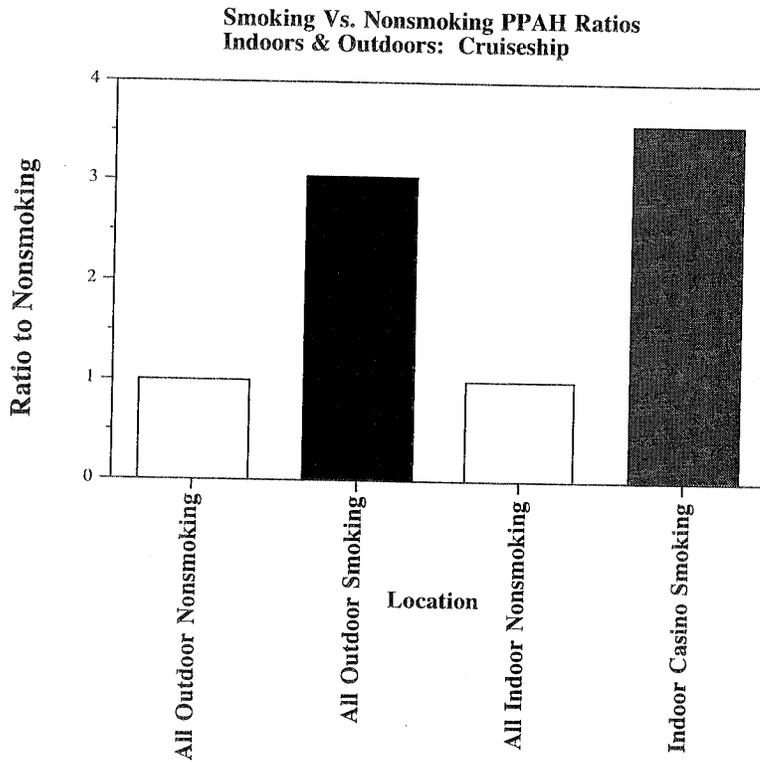


Figure 4. Weighted-mean ratios for all Outdoor Nonsmoking measurements to all Outdoor Smoking measurements, versus ratios of all Indoor Nonsmoking measurements to all Indoor Smoking measurements. Outdoor smoking on a cruise ship can expose nonsmokers to PPAH levels comparable to those in an indoor casino, suggesting that outdoor carcinogen exposures of nonsmokers from secondhand smoke are not low.

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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 is implicated in every 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/hs/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 - I. 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 addsmore 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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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 from 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 al. 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.

Kenneth G. Brown, Ph.D.

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Ms Janette Brooks, Chief
Air Quality Measures Branch
CA Air Resources Board
Environmental Tobacco Smoke
1001 I Street
PO Box 2815
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.

* 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 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 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 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?

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 consistent 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 actually "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.

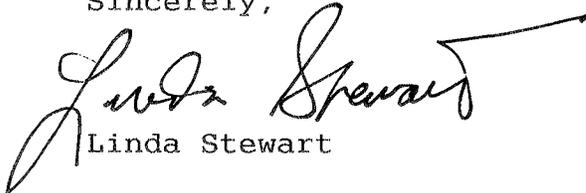
Now, climbing on top of that, OEHHA appears to estimate that virtually all lung cancer deaths among non-smokers are caused by ETS!? It hardly pays to ask upon what this is based.

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,

A handwritten signature in cursive script that reads "Linda Stewart". The signature is written in black ink and includes a long horizontal stroke extending to the right from the end of the name.

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.

March 25, 2004

MARY E. WARD
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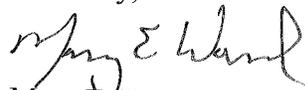
Ms. Janette Brooks
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
1001 I Street
P.O. Box 2815
Sacramento, California 95812

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 exposure² and health effects³ data for the substance and to specifically determine whether

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” in California. 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

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 al.*, 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

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,

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 active smoking (Terry 2002)²³ and omits one of the cohort studies (Nishino 2001) that examines ETS and breast

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

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

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.

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.

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.

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 TOBACCO 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 (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.

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.

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 (5) 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 $\alpha=0.05$, two sided), and statistical power (usually $1-\beta=80-90$) 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 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.

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 weakly, 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; Mitchell *et al.* 1997) are treated by OEHHA reviewers as if they were independent when in fact they were not separate studies. Instead they comprise one interim report, and three subsequent publications all stemming from the same SIDS case-referent study.

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). 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 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.

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 introduced 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.

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 HFS 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 Enstrom 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 FTS 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; 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).”

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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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. (LeFlorier 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. He 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 18 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 18 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 He 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 disproportionately 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 1200 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 He 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 14.9, 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 0.34 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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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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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 (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

Men -- 7758 CHD deaths^a
among never smokers.

Women -- 7133 CHD deaths^b
among never smokers.

Spousal Smoking	π	95% CI	Spousal Smoking	π	95% CI
Ex	0.95	(0.83-1.09)	Ex	0.99	(0.93-1.05)
current:			current:		
1-19	0.99	(0.89-1.09)	1-19	1.04	(0.97-1.12)
20-39	0.98	(0.85-1.13)	20-39	1.06	(0.98-1.15)
40+	0.72	(0.41-1.28)	40+	0.95	(0.78-1.15)
Any	0.97	(0.90-1.05)	P cigar	1.06	(0.99-1.14)
			Any	1.03	(0.98-1.08)

National Mortality Followback Survey
CHD/ETS Case-Control Study^c

Men				
Spousal smoking	Cases	Controls	π	95% CI
No	378	783	1.0	
Yes	97	215	0.97	(0.73-1.28)
Women				
Spousal smoking	Cases	Controls	π	95% CI
No	459	969	1.0	
Yes	455	961	0.99	(0.84-1.16)

LeVois and Layard (1995)

Layard (1995)

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)[†]

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. 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			
	<u>0-2</u>	<u>2-5</u>	<u>5-10</u>	<u>10+</u>
<u>CPS-II</u>				
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^a

	Current smokers	Ex-smokers		
		Years since quit		
		<u>≤1 year</u>	<u>1-2</u>	<u>3-5</u>
Men				
<u>6-10</u>				
<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, ≥ 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 1 and 2). 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 3). 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 (1,2,3,4).”

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. 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 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, including the results for coronary heart disease and lung cancer in the full CPS I. 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, 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 20-50%. 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:

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.

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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
Tiburon, CA

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,
Washington, DC.

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.

1979 to
1980 Health District Five Program Evaluation Services.
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.

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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 Institute, Division of Social and Preventive Medicine, Seminars on Current Issues in Epidemiology, Spring, 1988.

REFERENCES AVAILABLE UPON REQUEST



Michael J. Thun, MD, MS
Vice President for Epidemiology and
Surveillance Research

March 11, 2004

Janette Brooks, Chief
Air Quality Measures Branch
Air Resources Board
1001 I Street
PO Box 2815
Sacramento, CA 95812

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,

A handwritten signature in cursive script, appearing to read "Michael J. Thun".

Michael J. Thun, MD, MS

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 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 Assessment; 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 Assessment; 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

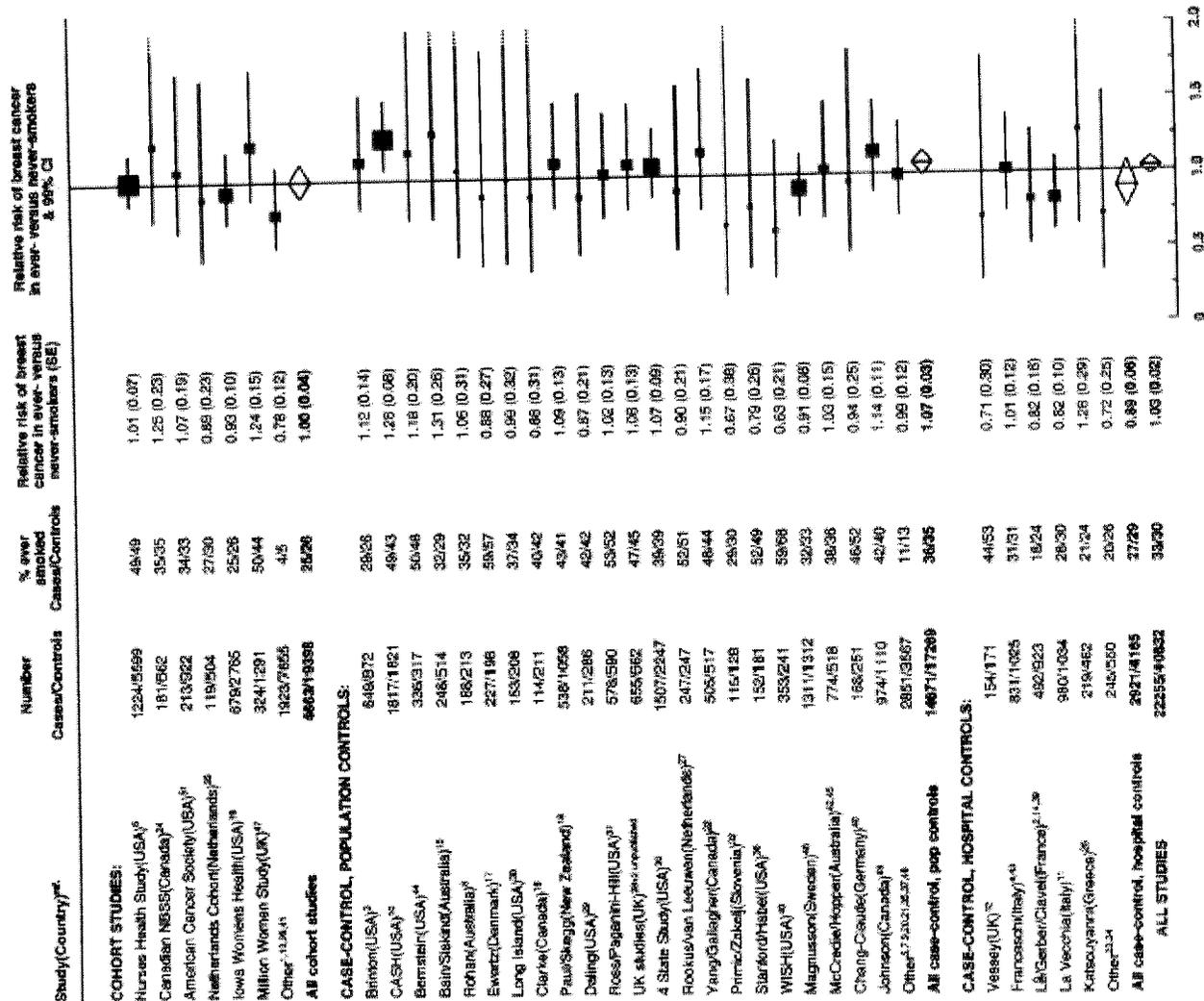


Figure 2: Breast cancer & ever smoking by subgroup

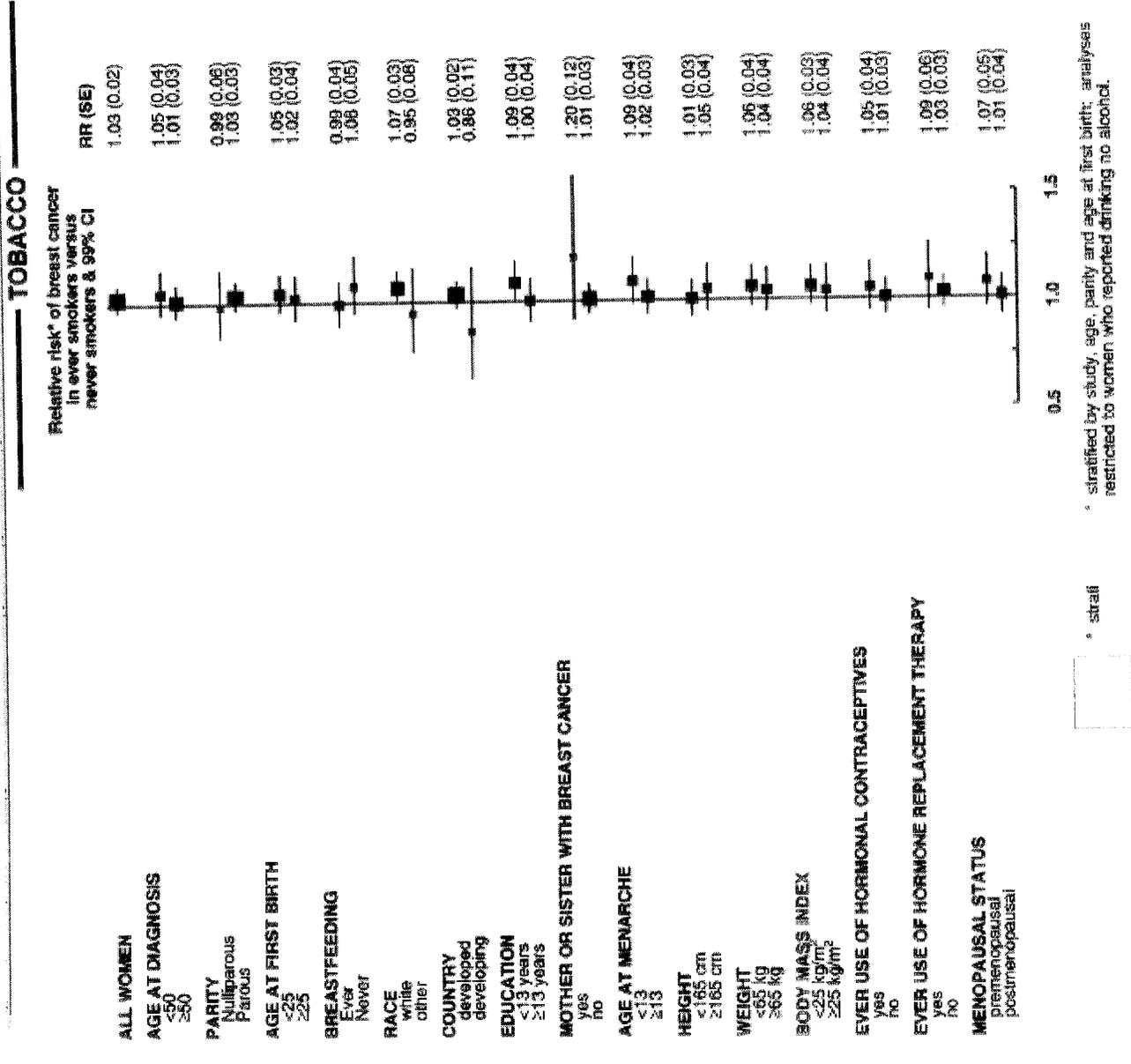


Figure 3. RR for Breast Cancer Among Current Active Smokers When Referent Group Includes (+) or Excludes (-) ETS Exposed Women

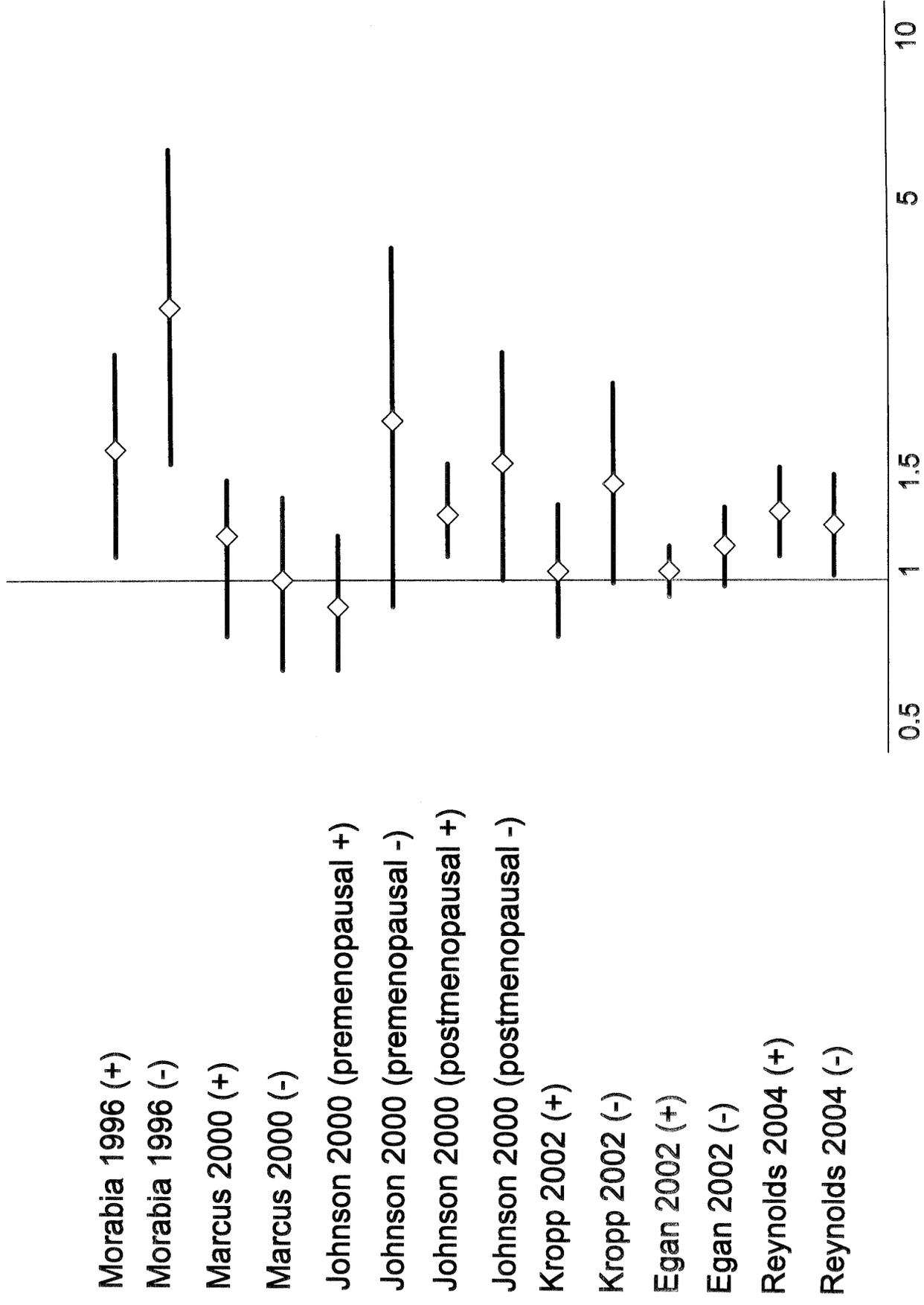


Figure 4a. NAT2 Susceptibility to Develop Breast Cancer from Current

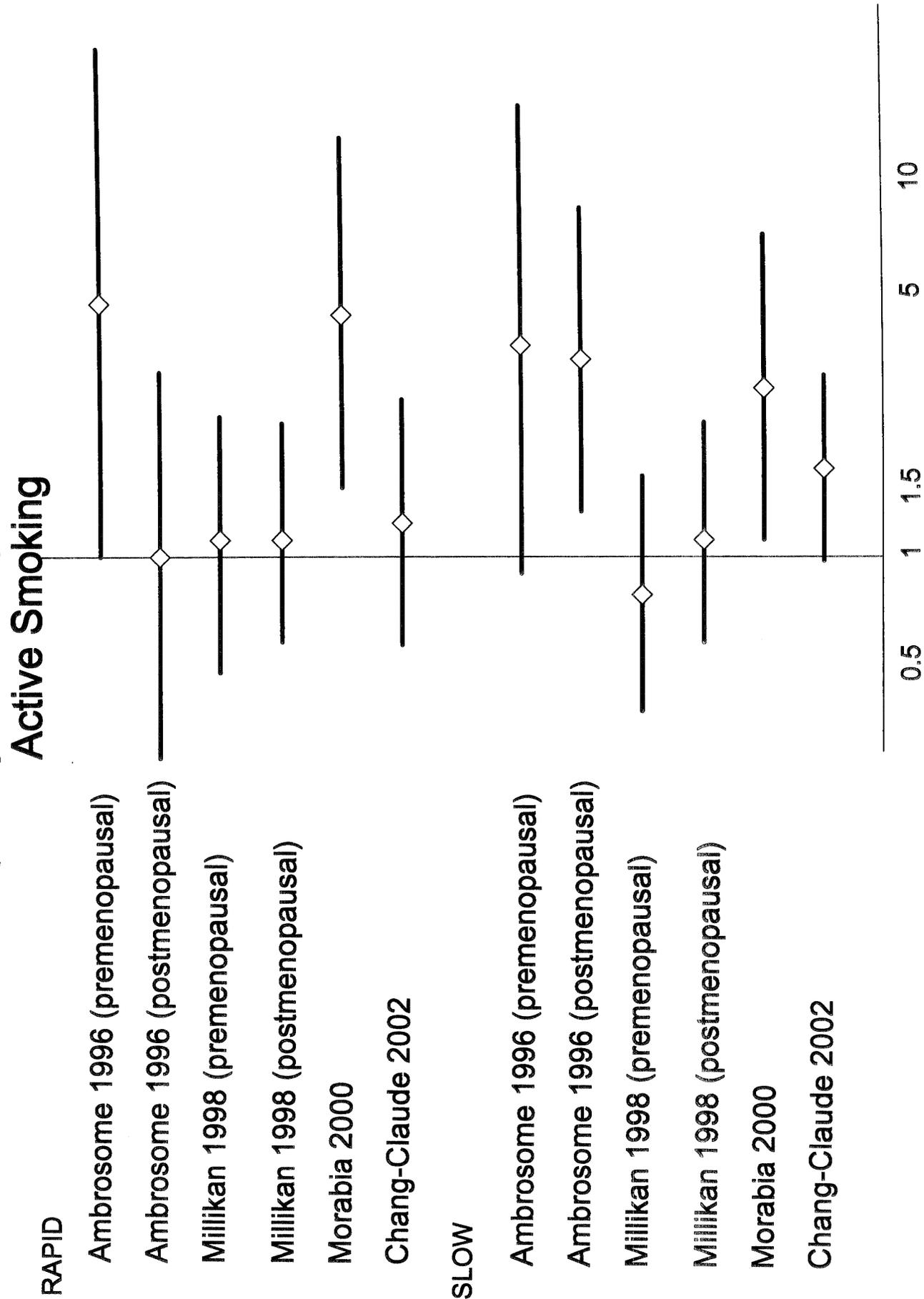
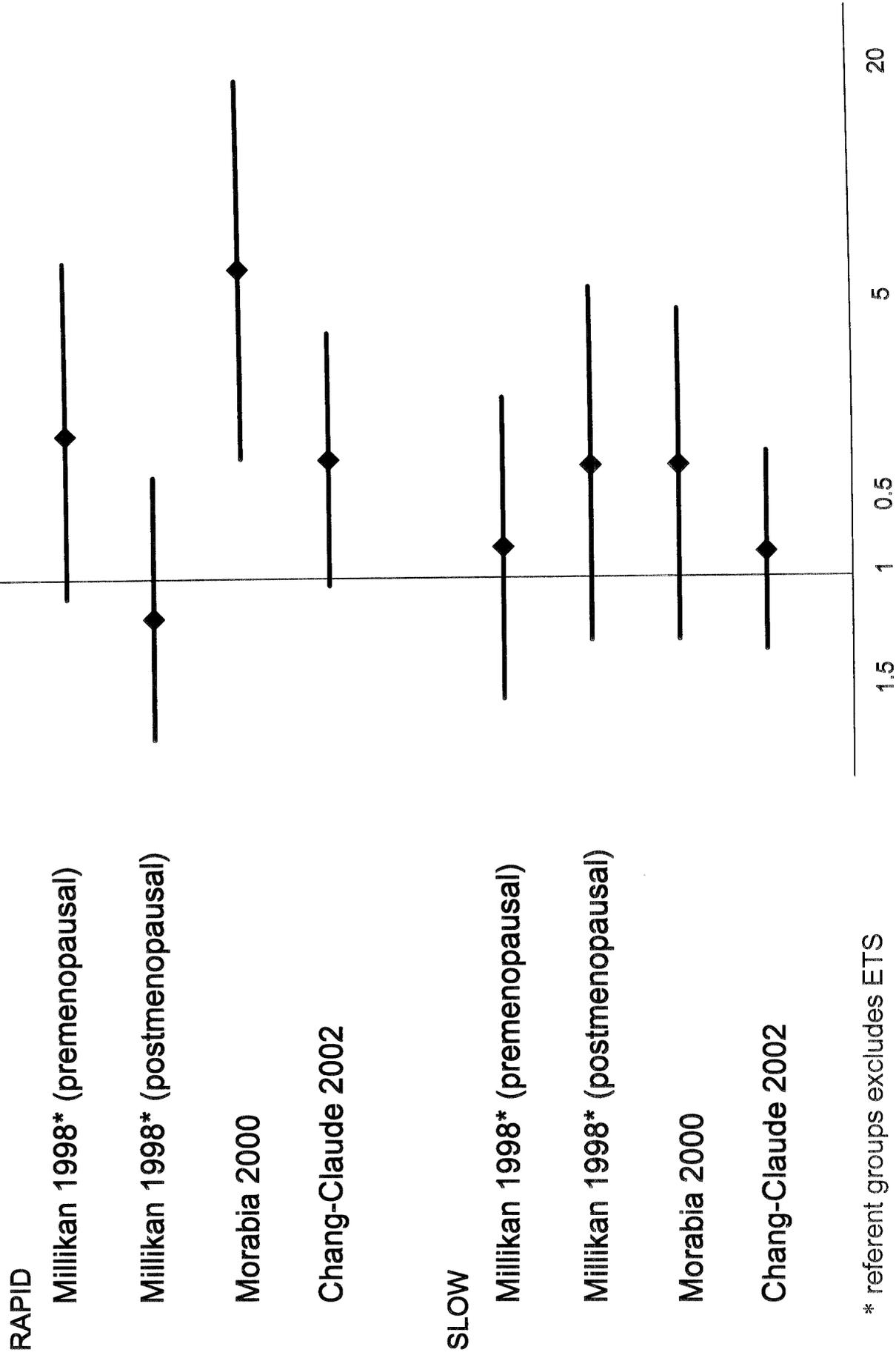


Figure 4b. NAT2 Susceptibility to Breast Cancer for Women ever exposed to ETS



* referent groups excludes ETS

Figure 4c. Genetic Subgroup Susceptibility to Breast Cancer from Current Active Smoking

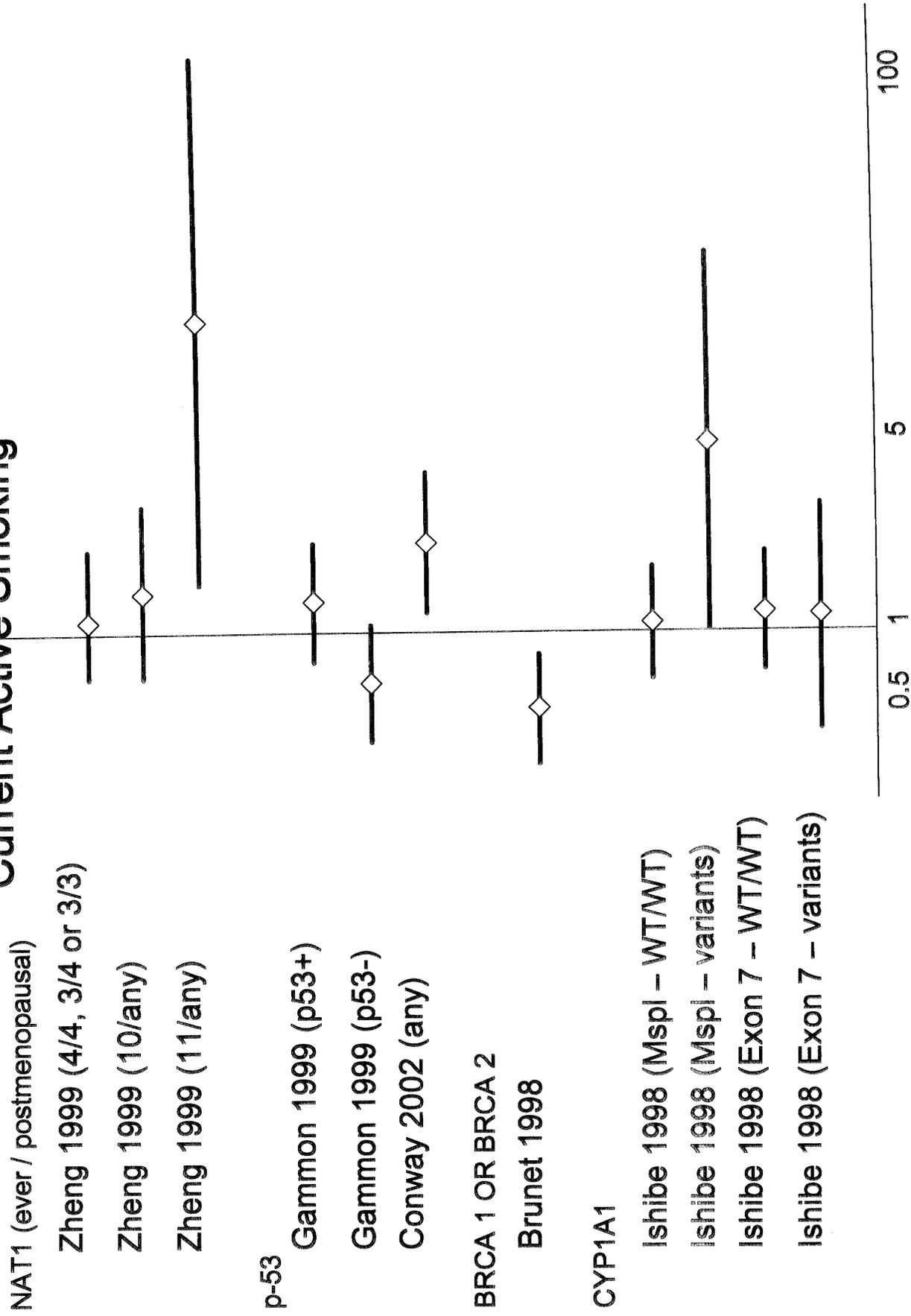


Figure 4d. Genetic Susceptibility to Breast Cancer from Current Active

Zheng 2002

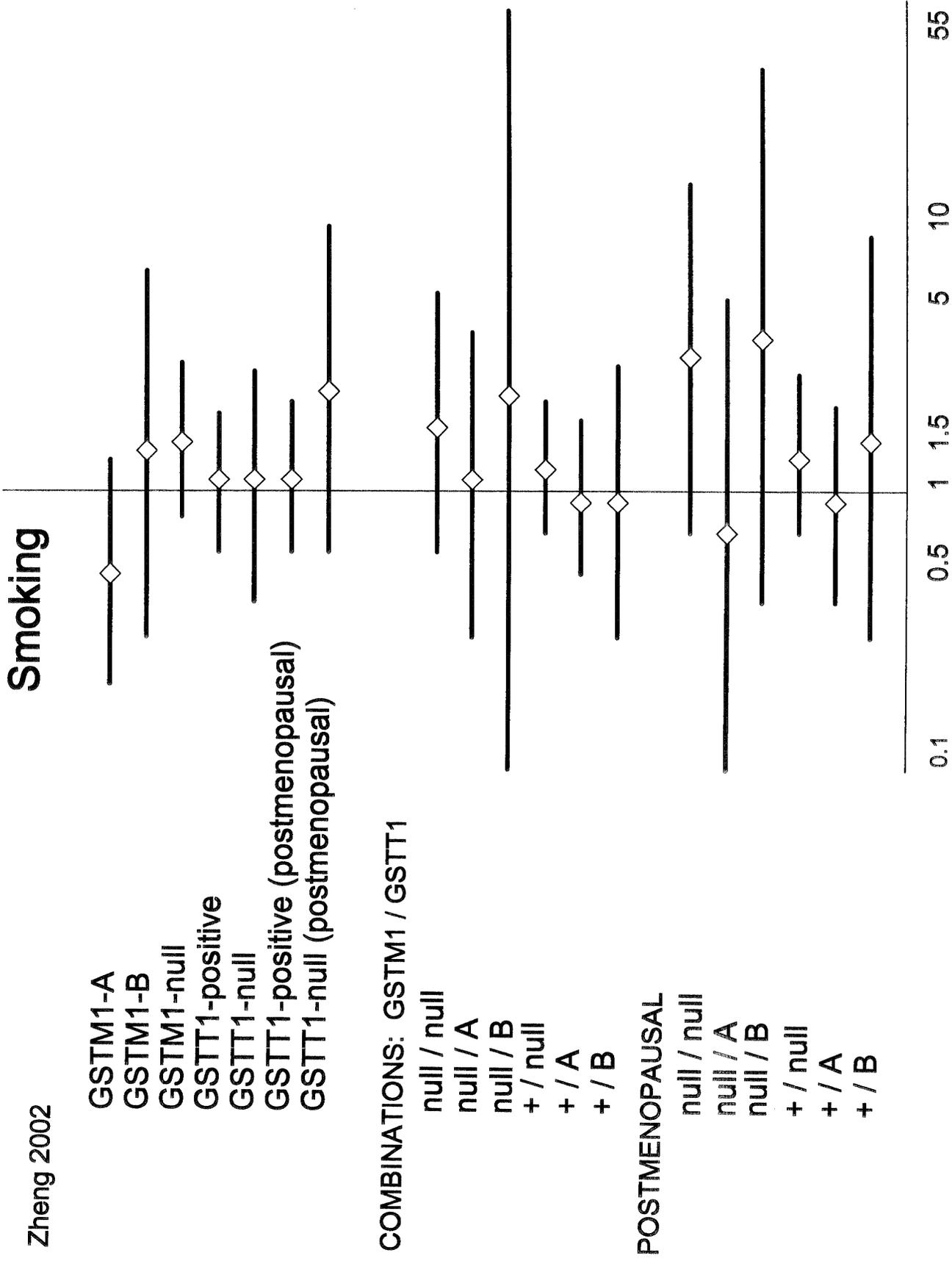
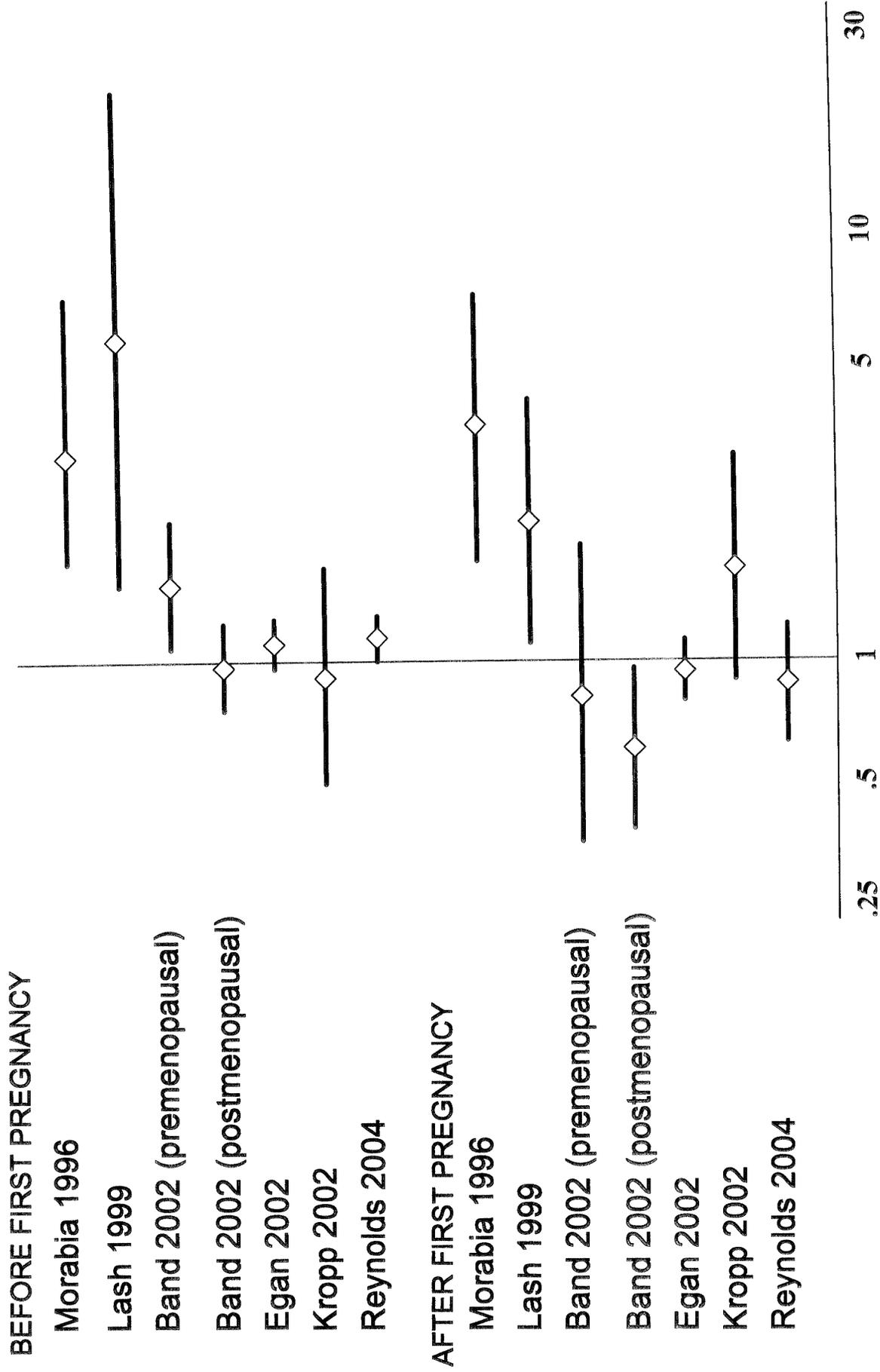


Figure 5. Timing of smoking and breast cancer risk



Comments on California EPA draft Health Effects Assessment for ETS

Michael J. Thun, M.D. (May 2, 2005)
American Cancer Society, Atlanta, GA.

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 (*I*). 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 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 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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Air Resources Board
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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 cotinine¹ 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 : I: 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 review². 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 review³.

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 cancer⁴.

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 published⁸⁻¹² 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-analyses¹⁴ 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 these¹⁷ the title concerns lung cancer but relevant data on cervix cancer are included. See my review⁶ 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 Cancer¹⁹ 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 review⁶ 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 review⁶ 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 review²⁸ 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 review²⁸ 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

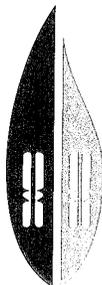
The Draft would improve from having some up-to-date meta-analyses. These are given in an enclosed document.¹⁴

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NATIONAL
CANCER
CONTROL
INITIATIVE

19 February 2004

Ms Janette Brooks
Chief, Air quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
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Sacramento, California 95812

Director:
PROFESSOR MARK ELWOOD
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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 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
Dr Ron Borland, QUIT Victoria
Dr Rosemary Knight, Commonwealth Government of Australia
Dr Judson Wells



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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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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,

A handwritten signature in cursive script, which appears to read "Robert T. Croyle", is written over a horizontal line.

Robert T. Croyle, Ph.D., Director
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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 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.

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
Chief, Air Quality Measures Branch
California Air Resources Board
Attention: Environmental Tobacco Smoke
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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

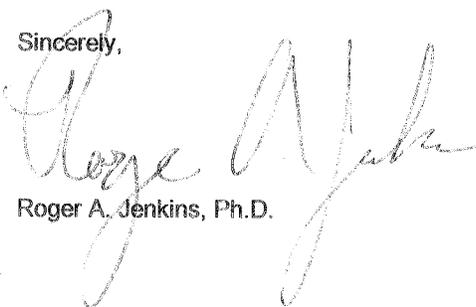
Attached herewith are my comments on the initial draft report mentioned above. Since my expertise is in the area of exposure science and analytical chemistry, I have provided comments only on Part A of the Report. In order to provide you some perspective regarding my comments, I have also included a 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”

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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 unsupported 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 there 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 $\mu\text{g}/\text{m}^3$. 24-hr TWA nicotine levels ranged from 0.0 – 5.66 $\mu\text{g}/\text{m}^3$. 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 $\mu\text{g}/\text{m}^3$, respectively, compares quite closely to that reported by Leaderer and Hammond (1991) of 44.1 and 2.17 $\mu\text{g}/\text{m}^3$.

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 $\mu\text{g}\cdot\text{hr}/\text{m}^3$. 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, median 15.5 hour personal exposure TWA concentrations for RSP were $21 \mu\text{g}/\text{m}^3$, and the 80th percentile value was $42.2 \mu\text{g}/\text{m}^3$. 95th percentile value was $88.3 \mu\text{g}/\text{m}^3$.

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 $\mu\text{g}/\text{m}^3$ 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 $66 \mu\text{g}/\text{m}^3$ and $82 \mu\text{g}/\text{m}^3$, respectively. 80th percentile levels of RSP were 117 and $228 \mu\text{g}/\text{m}^3$, 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 80th percentile RSP concentrations of 29.9 and $46.1 \mu\text{g}/\text{m}^3$, 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 $100 \mu\text{g}/\text{m}^3$.

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.

The “estimate” of RSP levels in homes (presumably smoking homes, although this is not called out) ranging from 300 – 5,500 $\mu\text{g}/\text{m}^3$ 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.

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.onrl.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 amount 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 $n\text{-C}_{27}\text{H}_{56}$.

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.

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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 TS RTP), 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 Contaminant (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

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,

A handwritten signature in cursive script that reads "Robert F. Phalen". The signature is written in black ink and has a fluid, connected style.

Robert F. Phalen, Ph.D.
Professor and
Director of the Air Pollution Health Effects Laboratory



March 03, 2004

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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 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.

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

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Ms. Janette Brooks
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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
Sacramento, CA 95812

**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 Kneprath, at (916) 442-4446 or pkneprath@alac.org.

Sincerely,

Susan Rappaport, MPH
Vice President, Research and Scientific Affairs
American Lung Association
61 Broadway, 6th Floor
New York, NY 10006

Paul Kneprath
Vice President, Government Relations
American Lung Association of California
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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.

Janette Brooks

March 4, 2004

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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

Assistant Superintendent

Learning Support and Partnerships Division

WB:jl



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,

A handwritten signature in black ink, appearing to read "William V. Corr". The signature is written in a cursive, flowing style.

William V. Corr
Executive Director