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Dear Dr. Enstrom,

Thank you for your June 21 letter requesting additional information from the American Cancer Society's Cancer Prevention Study II (CPS-II) on the relationship of environmental tobacco smoke (ETS) to lung cancer and heart disease mortality. You may be aware that we have published analyses from CPS-II on the relation of ETS exposure to both coronary heart disease (CHD) [1] and lung cancer [2]. These publications describe the mortality experience of over 300,000 married couples from their month of enrollment into CPS-II in 1982 through the end of 1989. With respect to heart disease, we found 22 percent higher death rates from CHD [rate ratio (RR) 1.22, 95% confidence intervals (CI) 1.07 to 1.40] among never smoking men married to currently smoking wives compared to those married to wives who did not smoke. The corresponding values for women were RR 1.10, 95% CI 0.96=1.27). These analyses controlled for age, body mass index, aspirin use, alcohol consumption, employment status, physical activity, and a self reported history of each of the following: heart disease, hypertension, diabetes, and arthritis). With respect to lung cancer, we found that the mortality rate was 20 percent higher among women whose husbands ever smoked during the current marriage than among those married to never-smokers (RR=1.2, 95% CI=0.8-1.6). For never-smoking men whose wives smoked, the RR was 1.1 (95% CI=0.6-1.8). These analyses controlled for age, race, years of education, blue collar employment, occupational asbestos exposure, self reported history of chronic lung disease (chronic bronchitis, emphysema, asthma, tuberculosis), and an index of fruit and vegetable consumption. The paper noted that even very large prospective studies have minimal statistical power (or precision) to measure relative risk values in the range of 1.2 for uncommon illnesses.

We have intentionally not extended our analyses of ETS exposure using longer-term follow-up of CPS-II (now complete through 2004), because the information on active smoking and ETS exposure has not been updated since the entry questionnaire in 1982. We do know that approximately half of the participants who reported current smoking in 1982, who later participated in the CPS-II Nutrition Survey in 1992 had stopped smoking during this ten year interval. If we were to rely on the 1982 data to classify ETS exposure from a spouse during long term follow-up of the full cohort (1.2 million), we would misclassify ETS exposure in at least half of the subjects who were originally exposed. In fact, the results of the analysis you request would be scientifically meaningless because of the lack of information on changes in exposure status. Furthermore, we cannot limit the long-term follow-up that you propose to the CPS-II

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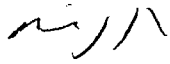
Nutrition subcohort, since despite it size (170,000 participants), only 10 percent of the subjects continue to smoke, and the number of lifelong nonsmokers whose spouses smoke is far too small to study the long-term effects of ETS.

The problem of misclassification of exposure is critical even in the short term when studying the relationship between ETS and heart disease, since the adverse effect of secondhand smoke on thrombosis occur acutely. You may recall that an article published under tobacco industry sponsorship reported no association between ETS and coronary heart disease in CPS-II [2, 3]. That analysis obscured the relationship between ETS exposure and CHD mortality by failing to report the results separately for never-smokers whose spouses continued to smoke and those whose spouses had stopped smoking. Their results were later repudiated when Steenland, Thun, et al. (1996) demonstrated that ETS was in fact associated with increased mortality from heart disease when the correct classification of ETS is used. However, the misleading results of LeVois and Layard have been widely publicized by the tobacco industry in its efforts to defeat community efforts to prohibit smoking in public facilities.

You and I have discussed the problem of exposure misclassification at length since March, 1998, when I strongly advised you against using your long-term follow-up of Californians in Cancer Prevention Study I to study ETS exposure because of the certainty of misclassification of exposure. The manuscript that you and Dr. Kabat ultimately published in the British Medical Journal had no information on secondhand smoke exposure between 1972 and 1998 (69% of the 39 year follow-up) for most of the cohort. It relied on information on one source of exposure (having a spouse who smoked) during the first twelve years. In so doing, it violated a basic principle of empirical evidence, that scientific findings are only as valid as the underlying measurements. The analyses that you are now requesting in CPS-II also violate this principle.

In summary, I do not believe that the analyses you request in CPS-II would produce scientifically meaningful results. To study ETS exposure over a 16 year follow-up without updated information on active smoking or ETS exposure would seriously compromise the validity of the exposure data. Unlike our published analyses from CPS-II on secondhand smoke, your proposed analyses will not control for any potential confounders other than age and sex. Not only would these results be scientifically uninterpretable, but based on past experiences, they may well be used by your sponsors in the tobacco industry to further mislead the public.

Sincerely,



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1. Steenland, K., *Passive smoking and the risk of heart disease.* JAMA, 1992. **267**: p. 94-9.

2. Cardenas, V.M., et al., *Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study. II.* Cancer Causes Control, 1997. **8**(1): p. 57-64.

3. LeVois, M. and M. Layard, *Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature.* Reg Toxicol Pharmacol, 1995. **21**: p. 184-91.