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Reviewer's suggestions for transmittal to author(s)

(Please do not comment here about whether the manuscript should be accepted).

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1. Some comment is desirable about the potentially adverse effects of the high refusal rate in the initial telephone survey, which the paper mentions.

2. The study addresses married women over the age of 18. It could be argued that the results relate to an age range different from the age range of the nonsmoking women married to smokers who have been the subject of most epidemiologic studies of the possible association of ETS exposure and lung cancer.

3. Salivary cotinine concentrations depend partially on the time of sampling during the day. In the study, sampling appears to have occurred (randomly?) throughout the day. Is it reasonable to expect that a natural randomization of sampling times may provide meaningful overall group differences? differences among cells? stratification of cotinine levels?

4. The reclassification of self-reported nonsmokers (and smokers) on the basis of cotinine is influenced to appreciable extent by individual metabolic patterns that appear genetically determined, and the proportion of other nicotine metabolites -- especially *trans*-3'- hydroxycotinine and its gucuronide -- that may cross-react in the RIA assay (Neurath & Pein, J. Chromatog. 415:400, 1987; Scheppers & Walk, Arch. Toxicol. 62:395, 1988; Cholerton et al., Lancet 343:62, 1994). Some of these and other studies have shown that a significant percentage of certified active smokers have cotinine concentrations *below* the established cutoff value for nonsmokers (Jarvis et al. Am J. Publ. Health 77:1435, 1987; Phillips et al., Environ. Intern. 6:693, 1994). The recent analysis of Cholerton et al (1994) is especially revealing of this peculiarity traceable to genetic factors, and which would reinforce the paper' conclusions.

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(The final sheet of this pack may be detached for your own records.)

EXCERPT(S) FROM SEPARATE
COMMENTS TO THE EDITORS
FROM REVIEWER B

REV (B)

The ogden study itself appears to me on first reading to be quite worthwhile since it is a large verification study and apparently well designed statistically. However, since the subjects were picked by mall-intercept and the interviews were actually conducted by a Reynolds' employed Ohio market research firm rather than epidemiologist interviewers, the results may be suspect. Reynolds ran smaller studies (not in the references) with similar recruitment designs in the past which were submitted to the regulatory agencies. They also have a large 16 city ETS personal exposure study, in conjunction with Oak-Ridge scientists, which estimates smoker-status misclassification rates as a subtopic. All these studies use, I think, the same market research firm to conduct the interviews. As a general observation these studies all have higher misclassification rates than those using other personnel.

1.

The study was not done as a basic research design; it was intended to estimate smoker-status misclassification rates in order

3.2

to produce bias estimates for downward adjustment of the relative risk estimates in the U.S. spousal ETS - lung cancer studies among female never-smokers. This is exactly what is done in the discussion section in its use on EPA's meta-analysis (pgs.-20-21). While the study can be presented independent of the arguments for bias, the authors make the bias arguments and application to the ETS-lung cancer studies and the EPA analysis a central part of their paper (see statement top of page 20 - "the misclassification bias (is) of greatest interest since it contributes the largest bias to observed risk estimates" - this should be removed). This leads me to question the age selection of this sample. Considering the large mean age differences in these misclassification rate studies (about 40 in this study vs. the mid sixties in the lung cancer case-control studies), the generalization of both its smoker-status misclassification rates and concordance rates to the U.S. ETS lung cancer studies would be highly suspect. While the EPA report criticized by the authors also used studies whose rates were less than ideal, those were the best available at the time. Considering the known purpose of this study, it is puzzling why no attempt was made to sample the proper age distribution.

In their abstract the authors claim that "these data indicate that misclassification bias alone is likely to explain any lung cancer risk elevation observed in the U.S. epidemiology of ETS exposure among nonsmoking women." This is an overstatement based on their analysis in the discussion section of pooled average relative risk estimates presented in the EPA report. Considering the large non-differential exposure misclassification downward bias, especially between the un- and lower-exposed groups, most of the increased risk observable is in the highest exposed groups, and this paper should acknowledge this. These small smoker-status misclassification bias estimates cannot explain the increased risks seen consistently in the highest exposure groups in either nearly all these U.S. studies or in the many non-U.S. studies. Dr. Ogden knows this and he should not be making these misleading analyses and misstatements in your journal. Furthermore, while the EPA used 1.09 as the smoker-status misclassification rate for the U.S. current smokers categorized as never smokers, bias estimates were calculated separately for the individual studies. Thus, I believe his Figure 4, if you allow him to include this analysis, would have to reflect this.

Since the authors want to use these misclassification rates to estimate misclassification bias in ETS-lung cancer studies, I feel they should clarify the difference between rates and bias in order to specify conditions for use of these rates in both the case-control and cohort studies. For example, in case-control studies differential misclassification rates between cases and controls could create very different biases. The large Fontham (1994) U.S. case-control study, specifically designed for minimizing smoker-status misclassification rates actually found lower rates in controls than in cases and both were lower than in this present study. In cohort studies the differential misclassification rates between the exposed and unexposed are important. This is a point

I thought was interesting in their paper - potential differential smoker-status misclassification rates among exposed vs. nonexposed nonsmokers. However, with such small numbers (Table 8), the conclusion on page 2 that "substantial differential misclassification was found between exposed and unexposed populations" is not justified. This is a merely an interesting suggestion. Perhaps additional analysis to determine whether these "deceivers" were also deceiving about their husbands' smoking would tell us more. Perhaps their answers on their own and their husband's smoking habits were just crossed or misread.

As a further consideration of Ogden et al study's intent to shed doubt on the studies showing increased lung cancer risk, I point out that this same study can just as easily provide estimates of exposure misclassification bias, a known downward bias in ETS-lung cancer studies. All that would be needed would be an analysis comparing cotinine levels by ETS exposure group (smoking vs. nonsmoking husbands) among never smokers, preferably by amount of spousal smoking (Fig. 3 presents the results for self-reported current smokers). Yet exposure misclassification bias is never even mentioned as a possible source of bias. I suggest that salivary cotinine levels by ETS exposure group for self reported never-smokers be presented analogous to Fig. 3. While the same claims of inapplicability to the lung cancer studies due to different age distributions are pertinent, this might somewhat alleviate claims of publication bias.

Considering your known reluctance to combining results from multicenter investigations in which the design is not a randomized clinical trial, you might also want to inquire about the internal consistency from the 9 cities before allowing the combined analysis. Personally, as long as they are statistically consistent and comparably conducted that part of the analysis is o.k. with me.

In general the paper is very well written and well organized, presents new evidence, and is clear enough to people familiar with the topic. I suspect you often face dilemmas about whether to publish studies whose intent is less to illuminate than to persuade.