

Reviewer's report

Title: Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study.

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Reviewer: Aaron Cohen

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General

Critical assessment of earlier studies of outdoor air pollution and lung cancer, such as the US American Cancer Society study (Pope et al. JAMA 2002), has focused on the possibility of residual confounding by cigarette smoking (Moolgavkar SH. A review and critique of the EPA's rationale for a fine particle standard. Regulatory Toxicology and Pharmacology 42 (2005) 123-144. The EPIC cohort study is the largest to date of never and former smokers, and therefore has the potential to more definitively address the issue of confounding by cigarette smoking than any previous study. Indeed control by restriction is probably the only way to address conclusively the problem of potential confounding of estimates of a small excess relative risk by a factor with a much larger relative effect (Cohen AJ. Air pollution and lung cancer: what more do we need to know? (Editorial) Thorax. 2003 Dec;58(12):1010-2). Control by restriction, however, sacrifices the ability to estimate joint effects, an issue of potential concern with regard to smoking and outdoor air pollution. These issues, and others noted below, need to be addressed in substantially greater depth and detail.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) The authors should present results for PM10 and (perhaps) SO2 as well as NO2. Apparently these data were collected. Have they been analyzed? What was found? A major European risk assessment (Kunzli et al. The Lancet 2000) used PM10 to quantify the effects of traffic-related air pollution, and the most recent follow-up of the US ACS study reported an association of inhalable PM (PM15) with lung cancer. PM results are important for evaluating this study in light of the rest of the literature.

SO2 has been used as an indicator of long-term exposure to stationary combustion sources in two Scandinavian lung cancer studies, which found no association. This should be replicated.

2) Restriction to never and former smokers has implications for estimating the outdoor air pollution attributable burden in Europe in that it precludes estimating the joint effects of active smoking and outdoor air pollution. The authors touch on this issue in the Discussion, but only as regards whether the EPIC cohort accurately represents European never and former smokers. Of equal or perhaps greater importance is the issue of the number of lung cancers due the joint effect of smoking and long-term exposure to air pollution. This quantity has not been able to be estimated with precision in other studies, but supra-additivity has been reported in several studies (Samet JM, Cohen AJ. Air Pollution and Lung Cancer. In: Air Pollution and Health. Holgate S, Samet J, Koren H, and Maynard R (eds.), Academic Press, London 1999.)

3) Joint effects of ETS and air pollution could have been estimated. Were they?

4) Authors should justify assertion/assumption that NO2 is only a marker for mobile source air pollution. Power plants and waste incinerators emit NOx.

5) Authors should justify and buttress with evidence the statement (page 8) that potential confounders have been "thoroughly controlled." The major argument in my opinion is that the main potential confounder, smoking, has been controlled by restriction. Other potential confounders (e.g., ETS, occupation, radon) pose less of a threat, but this needs to be argued quantitatively, not merely asserted. With regard to ETS, it appears that the air pollution regressions did not control ETS. If not, why not? With regard to controlling for the effects of occupation, the authors should note the results of the HEI reanalysis of the ACS (Health

6) Authors should justify and buttress with evidence the statement (page 8) that "information bias can be ruled out due the prospective design." Measurement error is an important form of information bias. Can it be ruled out? If not, what might its effect be on the estimates with regard to both direction and magnitude.

7) The authors should justify the view that "living near heavy traffic road" should be interpreted solely as an index of exposure to air pollution. Is it not possible that this metric represents other risk factors for lung cancer (e.g. SES)?

8) The Discussion should place the current results in the context of the larger literature on air pollution and lung cancer, not merely one recent risk assessment. For example:

What does new information does this study contribute? (Hint: control of confounding by restriction).

Are the current results consistent with previously reported effects in never/former smokers?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.