Reviewer's report

Title: Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer

Version: 1 Date: 30 April 2012

Reviewer: C. Arden Pope

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General Comments:

1. This is an ambitious attempt to provide a systematic review and meta-analysis of the epi evidence of smoking and lung cancer. It is restricted to studies with 100+ lung cancer cases and to studies in the 1900s. The large body of studies involved and the number and complexity of the issues make this a highly challenging undertaking. It is no small effort to just carefully review this analysis. The review has included a large amount of judgment calls (most of which are reasonably well documented) but many of which readers and reviewers could quibble with. There is also an element of “trust us, we’ve got this right” that is unavoidable in such a large and complicated review. However, in general I am impressed with the remarkable effort, the apparent attempt at comprehensiveness, and the systematic well-documented approach. I find this to be a well-written and extremely useful review.

2. Figures and Tables. Dense but well done and very informative.

Major Compulsory Revisions:

1. Page 2, Abstract. The results section of the Abstract (and to a large degree, throughout the report) the primary emphasis is on the heterogeneity of the results. While heterogeneity is well documented and should be included and discussed, for me the most overarching result is the remarkable consistency and coherency of the results. For me the results section of the Abstract should be completely rewritten to more closely reflect the way the results are summarized at the beginning of the Discussion section on page 45. For example, using the existing abstract and the text on page 45, a suggested rewritten results section of the abstract is:

Abstract Results:
A total of 287 studies (19 subsidiary) were identified. The review and meta-analyses demonstrated a clear and highly consistent relationship of smoking to overall lung cancer risk. A smoking-lung cancer relationship was observed for ever smoking (RR 5.55, CI 5.12-6.01), current smoking (RR 8.48, 7.68-9.36), ex smoking (4.30, 3.93-4.71), and only pipe/cigar smoking (2.92, 2.38-3.57). The smoking-lung cancer relationship was much larger for squamous cell carcinoma (RR for current smoking, 16.91, 13.14-21.76) than for
adenocarcinoma (4.21, 3.32-5.34). The smoking-lung cancer risk relationship was evident in both sexes (with somewhat higher RRs in males), in all continents studied (with RRs highest for North America and lowest for Asia, particularly China), and in prospective and case-control studies. That this relationship is causal was supported by evidence of a dose-response to amount smoked, duration of smoking, tar level and fraction smoked, and with earlier age of starting to smoke, and decreasing with duration of quitting. It is also supported by minimal sensitivity of RR estimates to amount of adjustments for covariates.

2. The analysis regarding publication bias seems incomplete, lacking context, and scattered. On page 45, the brief discussion of publication bias results is somewhat suggestive of publication bias. Yet the results are clearly mixed. First, there is a clear and well-documented selection bias in this review and meta-analyses. It is well justified to focus on the studies with a substantial number of lung cancer cases (100+). However, by doing so, tests of overall publication bias are less easy to interpret. Clearly the authors understand this issue. On page 52 as part of the discussion of “Number of cases”, they note the tendency for RRs to be higher in larger studies and also note that this tendency is in the opposite direction to that predicted from publication bias. They also note that the explanation is unclear. A similar discussion is given on page 58. I think that this issue should be addressed more directly. It may be true that if studies with less than 100 lung cancer cases were included, there may be compelling evidence of publication bias. However, my reading of this paper is that the evidence of publication bias is weak and/or mixed at best. If this is true, it should be clearly stated in the paper. If it is not (if the authors think that there is clear publication bias), the relative size of this bias should be addressed.

Discretionary Revisions:

1. Page 2, Abstract, Background. I think that it is a bit of an overstatement to state that “no systematic review exists.” Given the various Surgeon General and other reports and reviews that have been written, there are a number of systematic reviews that exist. Specifically what is the unique contribution of this report?

2. Page 2, Abstract and page 18. The sentence on tar levels in the abstract overstates the inferences allowed based on the limited number of studies, the enormous uncertainties regarding tar yields, etc. In the suggested abstract the tar results are only briefly mentioned as adding evidence to a dose-response relationship.

3. Page 27, The one-sentence paragraph just before “B. Risk from current smoking”. This one-sentence paragraph is awkward and unclear. Suggest rewrite and clarify.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.