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PNL/dpm

2 July 1992

Project Officer for Environmental
Tobacco Smoke
Technical Information Staff
Office of Health & Environmental
Assessment (RD-689)
U S Environmental Protection Agency
401 M Street, S W
WASHINGTON D C 20460
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Dear Sir,

At the request of the Tobacco Institute I am enclosing a commentary on issues relating to lung cancer in the May 1992 EPA External Review Draft, "Respiratory health effects of passive smoking ..." and 2 Annexes cited therein. I hope you find this material of value in finalising your document. If I can be of any further assistance in elaborating on and clarifying any of the points made, please let me know.

Yours faithfully,

Peter N Lee

encl.

"RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS"

A commentary on issues relating to lung cancer in the May 1992 SAB Review Draft

Author : P N Lee

Date : July 1st, 1992

Signed : P N Lee

Date : July 1st, 1992

*Any views expressed are those of the author and not of any other person or company

Summary of conclusions

This document provides a detailed critique of the second draft of the EPA report, giving particular attention to the evidence on lung cancer. The conclusions drawn are as follows:

1. The arguments put forward by EPA in section 4, which could equally well have been made 20 years ago, merely generate a hypothesis to be tested and do not of themselves justify classification of ETS as a group A carcinogen. ETS and mainstream smoke are not the same, exposure to many chemicals is orders of magnitude lower from ETS, and evidence from active smoking does not demonstrate absence of a threshold dose.

2. The epidemiological evidence also does not justify classification of ETS as a group A carcinogen. The evidence relating risk of lung cancer to spouse smoking in females does not provide convincing evidence that ETS causes lung cancer. The second draft of the EPA report has a number of major deficiencies.

   a) It totally underestimates the various possibilities of bias. Misclassification of smoking status is inadequately correlated for by an obscurely presented procedure, which is mathematically incorrect, involves numerous dubious assumptions, and ignores relevant data indicating a higher misclassification rate than that employed by EPA. The conclusions that confounding by other risk factors does not cause bias ignores extensive evidence which indicates

it does. Specific study weaknesses are noted, but no attempt is made to quantify the resulting bias. The possibility of publication bias is not even mentioned.

b) Evidence not readily fitting in with the hypothesis that ETS causes lung cancer is ignored or given little weight, while evidence that does fit in is overemphasised. The evidence that ETS is not associated with lung cancer risk in males or in ex-smokers is given little weight, and it is not even mentioned that in female never smokers lung cancer risk is not associated with workplace or childhood ETS exposure. Instead risk estimates derived from spouse smoking in female never smokers are assumed to apply to males, to ex-smokers, and to other sources of ETS exposure. 90% confidence limits are used, instead of the standard 95% limits, in an attempt to make even the spousal data statistically significant. The implausibility of some of the epidemiological findings, bearing in mind the much lower exposure to smoke constituents from ETS than from mainstream smoke, and the fact that some studies claim an effect for a type of lung cancer scarcely associated with active smoking, is not made clear.

c) The uncertainties are not at all adequately characterized. The range of lung cancer deaths attributable to ETS in the US is estimated to be between 2,500 and 3,300, implying considerable precision. This estimated range fails even to take into account sampling variation, which of itself

would reduce the lower limit to about zero. It also fails to account for variation resulting from uncertainty in the various parameter values used and assumptions made in the estimation process.

There are also a number of other deficiencies of the report, as discussed in these comments.

When commenting on the first draft of this report I concluded that it was substantially flawed and should be thoroughly reconsidered. Detailed examination of the second draft leads only to the same conclusion.

1. My background and qualifications

I am an M A of Oxford University, having read mathematics with postgraduate statistics. I am a Fellow of the Royal Statistical Society and an Honorary Research Fellow of the Institute of Cancer Research, Division of Epidemiology. I was employed as statistician and later as research co-ordinator to the Tobacco Research Council from 1966 to 1979. Since 1979, I have been an independent consultant in statistics and adviser in epidemiology and toxicology to a number of tobacco, pharmaceutical, chemical, and other companies. Since 1984, I have been director of P.N. Lee Statistics and Computing Ltd. I have had some 100 papers published, have contributed to two IARC monographs on analysis of animal experiment data, and have served as editor of standard reference books on smoking habits. I have been heavily involved in work on the possible health effects of environmental tobacco smoke over the last 10 years or more and have written two books on the issue, as well as many papers and letters on the subject. The EPA report itself makes numerous references to my work, including noting that I was the first to bring to attention the potential for bias due to misreported smoking habits - an issue that is given considerable attention in the report.

2. Introduction

In September 1990 I submitted detailed comments on the earlier, 1990, Review Draft of this report. As annexes to these comments I attached text and tables of "a detailed review of epidemiological evidence relating ETS to the risk of cancer, heart disease and other causes of death in adults who have never smoked", cited as a reference on page R-29 of the 1992 Review Draft. This has subsequently been published as a book, "Environmental Tobacco Smoke and Mortality", by Karger, Basle (1992), copies of which have been made available to EPA and the Scientific Advisory Board (SAB). In a number of places in this commentary I refer to my book as justification for points I make, referring to it as "my ETS book". The Review Draft commented on here is, for convenience, referred to as "EPA2" to distinguish it from the earlier draft.

In November 1991 I prepared a note, "Correcting meta-analyses of the association of lung cancer in females with spouse (or household) exposure for bias due to misclassification of active smoking status", which was also submitted to the EPA.

This document provides further comments on EPA2. It has taken into account some points I made on the earlier draft (EPA1), my contribution having been acknowledged on page xvii. However, a considerable number of fundamental weaknesses remain, such that it fails to justify the agency's conclusion that ETS should be classified as a Group A carcinogen. Clearly, the document requires further extensive revision.

3. Hazard identification II: Interpretation of Epidemiologic Studies on ETS and Lung Cancer (Chapter 5) and Population Risk of Lung Cancer from Passive Smoking (Chapter 6)

My comments relate mainly to these two chapters of EPA2 and to the Appendices which relate to them. Some other comments on EPA2 are presented in sections 4 and 5.

It is convenient, first, to describe briefly the various steps EPA2 goes through to reach its conclusion that "ETS is a Group A human carcinogen" and that "an estimated range of 2,500 to 3,000 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States". The main steps can be summarized as follows:

1) Select those epidemiological studies to be given detailed attention.
2) Select the index of ETS exposure (spouse smoking or nearest equivalent), and the sex (females) to be studied.
3) Choose the relative risk estimate considered most appropriate to each study.
4) Adjust, on a study by study basis, relative risk estimates downward to account for smoking habit misclassification using methodology developed by Wells and Stewart.
5) Use fixed effects meta-analysis, with 90% confidence intervals, to demonstrate the existence of a significant association between lung cancer and spousal smoking in Greece, Hong Kong, Japan and USA, but not in Western Europe or China.

6) Use trend tests to study the dose-response relationship.

7) Consider and reject confounding by other risk factors as a source of systematic bias in the studies.

8) Consider specific study weaknesses, and conclude (on pages 5-26) that "there are no additional sources of bias ..... that would systematically cause higher observed relative risk estimates" and that "the observed association between ETS and lung cancer cannot be explained by bias".

9) Reject the cigarette-equivalents approach for estimating population risk.

10) Restrict attention to the US epidemiological studies for the purpose of estimating population risk.

11) Adjust upward meta-analysis estimates of lung cancer risk associated with spousal smoking to take into account ETS exposure from sources other than the spouse ("background ETS") by a cotinine based Z-factor.

12) Use these risk estimates, coupled with independent estimates of relative risk for ever/never smokers and of population and total numbers of lung cancer deaths, to estimate mortality rates and numbers of lung cancer deaths associated with ETS among never smokers. By this method 1500 deaths per year, 470 from spousal ETS and 1030 from background ETS, are attributed to ETS exposure in never smoking women.

13) Assume mortality rates among never smoking men are increased to the same extent by ETS as they are in women and thus estimate

500 deaths per year, 80 from spousal ETS and 420 from background ETS, are attributed to ETS exposure in never smoking men.

14) Assume mortality rates among former smokers who have quit for at least five years are increased to the same extent as before, and thus estimate a further 1060 deaths per year are attributed to ETS, 440 in women and 630 in men (sic).

15) Recalculate deaths attributable to ETS based on relative risks and Z-factor estimates from the Fontham study, yielding a total of 2,500 to 3,300 deaths per year as against 3,060 deaths per year based on the 11 US studies.

In the sections that follow I comment on these steps in essentially this order, and also point out some omissions and give some general impressions.

3.1 Selection of epidemiological studies

My ETS book presented a detailed analysis of data from 28 studies which provided data for women, whereas EPA2 considers data from 30 (a 31st, KATA, being referred to in Table 5-1 but not actually producing any relevant data). EPA include three studies I did not. Two were very recent studies, FONT and LIU, only referred to as a "note added in proof" by me. The BUTL (Coh) study was only available as a dissertation, which I did not have, it being clear it was based on very few lung cancer deaths among never smokers. There is every reason for EPA2 to include these studies (though some weaknesses of FONT are described in section 3.20) but no valid

reason I can see to omit the second case-control study by Kabat which I included, which was reported at the 1990 Washington meeting of the Toxicology Forum, the proceedings of which are publicly available. Given the principal author is an SAB panel member, one would have thought it easy enough for EPA to get fuller details if they required them. It should be noted that it is a US study which produces a relative risk (RR) estimate less than 1, 0.90 (95% CI 0.46-1.76), which will slightly reduce meta-analysis estimates.

3.2 Restrict attention to females

It is clear that the data for females are based on far more deaths among never smokers and are presented in much more detail in the source papers than are the data for males. It is also clear (both from pp 146-150 of my ETS book and from pp 6-16 and 6-17 of EPA2) that the relative risk associated with spousal exposure in US males can readily be explained by a very modest amount of smoking habit misclassification (somewhat less than indicated by results from community based surveys), implying there is no actual evidence from the data in males of an underlying true association of lung cancer with spousal exposure. In these circumstances there are two main alternative ways to proceed:

(i) Use the data for males, both as a partial counterweight to the evidence in females in evaluating whether ETS causes lung cancer and directly in the estimation of deaths due to ETS in nonsmokers.

(ii) Ignore the male data and use female-based ETS risk estimates to estimate risk in males.

EPA2 has used the latter approach, and has even argued that this may underestimate deaths since males are probably exposed to more background ETS exposure than females. Although some 1000 of the total of 3000 annual lung cancer deaths they attribute to ETS are in males, they only attribute a range as narrow as 800 to their overall estimate (of 2500 to 3300 deaths). In other words they totally ignore what the actual male data are telling them, that there may in fact be no deaths attributable to ETS in males. In my view this is the wrong approach. EPA should have been totally "up front" giving the male data alongside the female data, showing under varying degrees of assumed misclassification what the corrected relative risk would have been, and taking full account of the uncertainty resulting from this in their final estimates.

3.3 Restrict attention to spousal smoking data

As is made abundantly clear in my ETS book, although the crude data (i.e. unadjusted for misclassification) suggest an association of spousal smoking with lung cancer risk, they show no association whatsoever with indices of ETS exposure at work or in childhood. Based on 13 independent relative risk estimates for workplace exposure and 11 for childhood exposure I estimated (on pp 117-9) by meta-analysis combined estimates of 0.98 (95% limits 0.89-1.08) for workplace and 0.98 (95% limits 0.86-1.12) for childhood exposure. EPA2 does not even consider such data or acknowledge that they show no association. There is no discussion at all in the report as to

why attention should be concentrated on spousal exposure. The evidence on workplace exposure should be subject to little or no bias due to smoking habit misclassification, which gives it advantages over spousal smoking as an index in some respects. Clearly, concentrating on one index that does show an association at the expense of two other indices that do not must bias interpretation of the overall evidence, regardless of whether the data for the first index are somewhat more abundant than for the other two. In my view the workplace and childhood data are crucial to understanding the whole evidence and must not be ignored. It is ludicrous, in particular, to attempt to estimate risks of non-spousal exposure to ETS indirectly (from evidence from spousal exposure coupled with evidence from relative cotinine values in women married and not married to a smoker), and to ignore totally direct evidence that actually is available on other sources of ETS exposure. In 1986, when nearly all the published data related only to spouse smoking as an index, it was understandable to concentrate only on this, as the National Research Council (NRC) and US Surgeon-General (USSG) did. Now, this is manifestly not the case and it is a very serious weakness of EPA2 that it does so.

3.4 Have the most appropriate relative risk estimates been used?

Section 5.2.1 of EPA2 is intended to explain the criteria used to select one spouse smoking relative risk estimate from another, where one study provides multiple estimates. In fact, it is quite unclear. Because "spouse ever smoked" is the most common index of ETS exposure one would have thought it logical, to minimize

between-study heterogeneity, to choose an index as close to this as possible where a choice is available, but it is not clear that any such decision rule was used. I went through the Tables in EPA2 and compared them with corresponding tables in my ETS book (all entries for which were independently checked back to source). Quite a number of minor differences were noted, but I will limit attention here to the larger differences where it seems that EPA have used an inappropriate RR value in their meta-analyses.

GARF - Why did EPA use 1.31 for the crude estimate, based on "husband's smoking habits at home" when the alternative of 1.23 based on "husband's total smoking habits" given in Table 5 of the source reference is clearly more appropriate for comparability with other studies?

JANE - Why did EPA use 0.86 for the crude estimate, based on ETS exposure in adulthood rather than estimate, as I did, a weighted average of the estimates of 0.93 and 0.44 for direct and surrogate interviews? As described on p 102 of my ETS book I obtained an RR of 0.75 with 95% limits of 0.47-1.20 for females.

LAMW - I would have thought it better to use the RR value of 2.01 for adenocarcinoma/spouse, than to extend the exposure criterion unnecessarily to include sources other than the spouse.

SOBU - Again I would have thought it better to use the data for spouse exposure than to include other sources of exposure unnecessarily. 1.13 is a more appropriate estimate.

Had more appropriate estimates been used for GARF and JANE, and had the second Kabat study been included meta-analysis relative risk estimates would have reduced (see section 3.5 and Table 1).

3.5 Has adjustment for misclassification been properly conducted?

A key feature of EPA2 is the conclusion that, after adjustment for misclassification of smoking status, the overall US data relating spousal smoking to lung cancer show a statistically significant relationship with Table 5-8 giving a relative risk estimate, adjusted for misclassification, of 1.19 with 90% confidence limits 1.04-1.35, equivalent to 95% confidence limits of 1.01-1.38.

Following considerable earlier published work on the subject, I examined, in my ETS book, the issue of misclassification at great length (pp 142-164). I presented estimates, for each study, of the degree of bias that would be produced, assuming no effect of ETS, of given proportions of typical ever smokers claiming to be never smokers. For a typical scenario for US women, I estimated that a 1% misclassification rate would produce a bias of 1.070, a 2% misclassification rate would produce a bias of 1.148, and a 3% misclassification rate would produce a bias of 1.236. Having presented a detailed review of available material on misclassification rates and on concordance rates, I concluded that for US populations it does not seem unreasonable to assume that something like 5% of ever smokers deny smoking. Because these

misclassified ever smokers do not have the lung cancer risk reported for average ever smokers (partly because ex-smokers deny smoking more than current smokers, partly because ex-smokers who deny smoking tend to have given up longer ago than average, partly because current smokers who deny smoking smoke less than average), I estimated this 5% was equivalent to about 2% of average ever smokers denying smoking. Taking into account the underlying variability and the uncertainty behind the various assumptions, I concluded that misclassification of smoking status could largely and perhaps completely explain the observed unadjusted association of ETS with lung cancer in US women, which at that time, before the appearance of FONT, I estimated at 1.11 (95% confidence limits 0.92-1.33).

Subsequently, in November 1991, I prepared a document (which was transmitted to EPA and is referred to on pages B-4 and R-29 of EPA2), which described a method for adjusting observed spouse smoking relative risks for smoking habit misclassification (as distinct from estimating bias assuming no true ETS effect). This method required input of:

i) study-specific data giving the two by two table for the spouse smoking/lung cancer risk relationship, and giving the risk reported for active smoking,

ii) assumed values of the misclassification rate of ever smokers as never smokers and of the husband/wife concordance ratio, and

iii) specification of whether passive smoking and active smoking posed additive or multiplicative risks.

Based on data from 11 US studies (now including FONT, but with Kabat 1990 in and the small BUTL cohort study out), I estimated, assuming a misclassification rate of 2%, a concordance ratio of 3.0, and a multiplicative model, that the relative risk unadjusted for misclassification of 1.18 would reduce to 1.04 (95% limits 0.89-1.21). Increasing the concordance ratio to 4.0 (well within the range of acceptable values from my review) would reduce the relative risk estimate further, to 1.01. (Assuming a concordance ratio of 3.0) a 1% misclassification rate would reduce the unadjusted estimate to 1.11, while a 3% rate would reduce it to 0.96. Even 0.5% misclassification would make the relative risk become statistically non-significant (1.15, 95% limits 0.99-1.33).

Table 1 summarises study by study the US results using my method and that of Wells and Stewart using methodology described in Appendix B of EPA2. There are a number of points to note:

(i) Both methods adjust on an individual study basis. The assertion on page 5-7 of EPA2 that only Wells and Stewart have done so is erroneous. All the early work, by Wells, by Wald, and by myself used a single adjustment to the overall risk estimate. My submissions in regard to EPA1, two years ago, contained results of analyses using study-by-study adjustment.

(ii) The adjusted meta-analysis relative risk of 1.19 given in Table 5-8 of EPA2 seems actually to be incorrect, given the

data cited there for the 11 studies. I can reproduce all the meta-analysis relative risks in Table 5-8 except that for the US. There appears to be an error that needs resolution.

(iii) The differences in the ETS data included do not make an enormous amount of difference - my unadjusted meta-analysis estimate of 1.18 is only slightly less than that of 1.22 for the EPA data.

(iv) The main difference is in the extent that smoking habit misclassification is estimated to reduce the relative risks. There are various possible explanations for this which are pursued below.

One source of difference in estimated misclassification bias is the fact that for some studies there are differences in estimates of the active smoking relative risk. Thus I used higher estimates for GARF (Coh) and KABA, and lower for CORR and WU. There were also (not shown) some differences in the assumed percentage of smokers, though differences were smaller. As a test of the importance of this, I reran my analysis using EPA active smoking (and percent smoking) data. This gave a somewhat higher meta-analysis estimate of 1.08, the difference being mainly due to the large GARF (Coh) study, which was now only adjusted down to 1.14, and not to 1.02.

Even after taking this into account, however, it was clear that the Wells/Stewart approach had produced less adjustment (down from 1.22 to 1.17, a 4.1% reduction) than had mine (down from 1.18 to 1.08, an 8.5% reduction).

As my approach produced about twice the adjustment of that of Wells and Stewart (even after using their data on active smoking), I reran the analyses assuming a misclassification rate half as high, i.e. 1%, to see if my answers then aligned with theirs. Table 2 compares the percentage reductions under the two methods. Although there is an obvious correlation between the two sets of percentages, there is still quite a considerable discrepancy for some studies, e.g. for FONT Wells and Stewart give a correction only about half of mine (i.e. equivalent to about 0.5% of ever smokers denying ever smoking), while for JANE they give a correction which is about double (i.e. equivalent to about 2% denial).

Though these comparisons indicate that in general Wells and Stewart have assumed a misclassification rate about half the rate I have assumed, they also indicate that the actual mathematical methods used may differ relevantly.

The method of Wells and Stewart (which has never, to my knowledge, been peer-reviewed) is actually extremely unclearly explained in Appendix B, so much so that in Annex A to this document I have attempted to clarify it. In this Annex, I show that there are an extremely large number of assumptions and parameters involved, much more so than in the much simpler (and exact) method I described in my November 1991 document. Furthermore, the parameter estimates used are often unreliable, due to lack of good relevant data. Even had the actual methodology been totally correct, there

would have been considerable uncertainty about the adjusted estimates. However, as is made clear in Annex A, there are also a number of errors in the Wells/Stewart method:

(i) It has been assumed that risk associated with exposure to husbands' smoking multiplies the risk associated with former smoking, but has no effect whatsoever on the risk associated with current smoking.

(ii) The multiplicative model in relation to ETS and to former smoking has been applied to observed risks when it would only apply (if it were appropriate) to true risks, i.e. risks not attributable to misclassification.

(iii) The estimated relative risk associated with current (versus never) smoking has been applied in the procedure to current regular smoking. Current smokers include both regular and occasional smokers.

(iv) In estimating the observed smoking habit distribution of the cases, the frequency of all former smokers (long-term and short-term) has been multiplied by a risk factor derived for long-term smokers only.

(v) The actual method of estimating the numbers of never smokers corrected for misclassification, given the observed distribution of cases and controls by self and spouse's smoking habits and given the assumed misclassification rates, is mathematically erroneous.

The other reason for the difference between my conclusions and those of Wells and Stewart arises from the actual data assumed for misclassification of current smoking status.

Table 3 compares data from Appendix B (Table B3) and from my ETS book (Table 3-34) concerning misclassification of current smoking. Based on 16 studies I obtained an overall estimate of 3.7%, twice as high as the 1.8% of Wells. The difference between the estimates is not because I used data for both sexes and he used data for females only since, for the studies of Coultas, Cummings, Lee and Pierce, my sexes combined rates are very similar to Wells' female rates. The difference mainly relates to which studies have been included, and my data set is much more extensive than Wells'. One of the studies I cite is that of Haddow (1987), and Wells amazingly says "the authors state (private communication from Dr George Knight) that the data from the study should not be used for misclassification studies" without giving any clue as to why not! A new form of publication bias is evidently not to include data from any studies the author tells you to exclude! Excluding this study in any case makes little difference, reducing a rate of 3.7% to 3.6%.

My general impression is that Appendix B is an obscurely written document which describes a statistical method for smoking habit misclassification adjustment which is to some extent mathematically in error and which depends on a whole host of inadequately explained and justified assumptions and imprecisely

known parameters. Various relevant studies providing evidence on misclassification are ignored and the effect of misclassification is likely to be greater than Wells' analysis indicates.

In my view, it would be preferable to use the method I describe, which is simpler and involves fewer assumptions, and to show how the overall meta-analysis relative risk estimate for the US depends on various assumed levels of misclassification (e.g. 0.5%-2.5%) and of concordance (e.g. 3-5), supported by data that these are reasonable ranges based on existing evidence. This would give a much better understanding of the uncertainties involved.

One other concern I have is that Wells and I have been involved in this issue for many years and are seen by some as putting over two radically disparate viewpoints. There seems to me to be a case for involving one or more independent statisticians of repute, not close to the ETS issue, who could hear in detail what Wells and I have to say, and who would make their own decisions regarding appropriate methodology and data. This would give a much more balanced impression to the document.

3.6 Is use of 90% confidence intervals appropriate?

Earlier major reviews of the evidence on ETS and lung cancer, such as by the NRC or USSG, followed generally accepted practice and used 95% confidence intervals and the EPA followed this precedent in EPA1. It is notable that in EPA2 a switch has been made to using 90% confidence intervals. This switch comes over to me too much as

if the authors were doing everything in their power to have the US meta-analysis relative risk come out as statistically significant, and I do not think regulatory authorities should come over in this way. In my view, use of 90% confidence intervals is only appropriate where it can be determined a priori that if there is an effect of ETS it can only possibly be in one direction. In practice this is rarely the situation, and although some will argue it is the situation here, I doubt if our knowledge of low-dose exposure is adequate enough to be sure. In any case with various potential biasing factors about, relative risks significantly below unity may actually occur.

One minor point is that in some tables mixtures of 90% and 95% intervals are used. This is just confusing. Since it is absolutely trivial to convert one to the other, there is no reason whatsoever not to do this.

3.7 Is fixed-effects meta-analysis appropriate?

In Table 5-8 the results of studies are combined over country or continent by what is sometimes termed fixed-effects meta-analysis, which involves calculating a weighted mean, using as weights the inverse of the variance of each odds ratio. Such a procedure takes into account only within-study variation. As noted on page 5-10 of EPA1 there is an implicit assumption of homogeneity of relative risk within the studies being combined. But it is abundantly clear, from a simple examination of Table 5-8, that this assumption is not supported by the data. The results for Hong Kong

and for China are certainly statistically heterogeneous and taken as a whole the data show significant heterogeneity. In these circumstances it is usual (see e.g. Fleiss and Gross (1991) and de Simonian and Laird (1986)) to allow in the calculations for the possibility of between-study variation being greater than expected, using a random effects analysis. This results in an increase in the size of the confidence intervals of the combined estimates. At the very least, EPA should explain in detail why they failed to take into account any element of the significant between-study variation in their meta-analysis.

3.8 Should WUWI and LIU be considered separately?

EPA2, on page 5-10, argues that the two Chinese studies of WUWI and LIU are less likely to detect any true passive smoking effect because of the presence of indoor smoke from cooking and heating (in the case of the LIU study with smokey coal, known to cause lung cancer). Implicit in their argument is the belief that ETS and indoor smoke are not independent risk factors which act multiplicatively (otherwise there would be no special problem in detecting a potential ETS effect) but are factors which act in a similar manner, so that their effects are additive. In this situation it is true that the relative risk in relation to ETS exposure would be expected to diminish with increasing exposure of the population to indoor smoke. But it is also true that, if this is the situation, the techniques of meta-analysis used are inappropriate, since they are designed to estimate a constant proportional increase in risk in the different studies. To produce

combined estimates would require either special adjustment study-by-study for level of exposure of the population to indoor smoke from other sources or combining differences rather than ratios of risks. It is still possible to produce tests of the null hypothesis but rather more difficult to produce valid combined estimates. I am surprised that EPA do not appear to have thought of this problem at all, or are they assuming that in all study populations except for WUWI and LIU (even for GAO and GENG) any effect of indoor smoke is negligible? Is this justifiable? The whole argument hardly makes sense anyway, if one considers the data presented in Table D-3 of EPA2 which shows that the estimated lung rate attributed to baseline sources was not notably high in WUWI.

The special pleading put forward by the EPA in regard to WUWI and LIU is an explanation why the relative risk should be lower in these than in the other studies. However, if ETS affects risk of lung cancer, the relative risk should still be greater than one. In fact, both studies give a relative risk estimate less than one, and in the large WUWI study the covariate adjusted relative risk is significantly less than one. The fact that this provides evidence against an adverse effect of ETS is not even mentioned by EPA and biasses the overall argument.

3.9 Use of trend tests

Section 5.3.2.3. of EPA2 is inadequate in a number of ways:

(i) It does not mention the fact that many of the sources of bias discussed, such as misclassification and confounding, would be

expected not only to result in an artefactual association but also in an artefactual trend. For example, Lee (1987) demonstrated a clear tendency for heavy smokers to be more likely to marry smokers than are light smokers. Indeed, on page 5-43 it is stated falsely, and without any supporting argument, that a dose-response "would be an unlikely result of any operative sources of bias or confounding".

(ii) It does not make it clear that the test for trend to some extent duplicates the test for an association comparing the overall ETS exposed and non-exposed groups. In LAMT, to cite only one example, the trend is significant despite the risk in the three exposed groups being very similar. An independent test would be to consider whether, within the exposed groups, risk rises with increasing dose. Layard (1990) calculated that none of the studies published up to that time has individually shown a statistically significant trend when calculated in this way.

(iii) It is incorrectly stated that "dividing the data into small exposure categories" (as in a trend test) "decreases the power to detect a real effect". If there is an association between lung cancer risk and extent of ETS exposure, and if the exposure index is correlated with actual exposure, the trend test is more powerful, not less. This argument that the results of the trend test are "especially compelling" is therefore false.

3.10 Confounding by other risk factors as a source of systematic bias

I find the section on potential confounders, 5.4.2, to be one of the weakest parts of the whole of EPA2. There are two major reasons for this. The first is that the apparent objectives are wrong. As judged by the second paragraph of 5.4.2.6, a single confounding variable is seemingly required to explain fully the significant association of ETS exposure with lung cancer in Greece, Hong Kong, Japan and the United States, before it is to be considered relevant. Why should it not be part of the story only, with other confounders and other sources of bias also relevant? The second is that, for no good reason whatsoever, the document limits attention only to evidence from the epidemiological studies of ETS and lung cancer. There is a massive literature showing that various occupations increase risk of lung cancer (many are cited as definite causes by IARC and other authorities) but this is not referred to at all. There is also a massive literature on diet as a protective dietary factor and lung cancer and Section 5.4.2.6. scarcely echoes the conclusion of a recent review by Fontham (1990) that "The dietary studies have been notably consistent, finding an approximate 50% reduction in risk associated with high compared to low consumption of carotene-containing fruits and vegetables". This is despite the obvious difficulty in getting good dietary data which would tend to underestimate the true effect of diet. There is also good evidence that family history of lung cancer is an independent risk factor for lung cancer. (I am currently finalizing a review paper which concludes that the data show an approximate doubling of risk, that does not seem explicable in terms of confounding by age,

smoking, family size, or other variables, and has been seen in studies where recall bias can probably be ruled out as an explanation). The impression given by EPA2, therefore, that these are not true lung cancer risk factors at all is most misleading.

In my ETS book, I presented on pp 133-142, detailed arguments why I believed confounding by diet and perhaps by other factors was relevant. I recommended that more work was needed to clarify the role of confounding more precisely. Though much work still remains to be done, I present in Annex B an interim analysis of data from a representative population of 9,000 men and women in the UK. From this analysis four general conclusions were reached:

1) Current smokers differ significantly from never smokers in exposure to a variety of independent risk factors for lung cancer.
2) The difference is virtually always in the direction of predicting an increased risk of disease in smokers independent of their smoking.
3) Where such a difference is seen, a difference in the same direction is nearly always seen in relationship to passive smoke exposure.
4) For many risk factors, the magnitude of the difference in exposure in relation to passive smoking is sufficient to cause bias large enough to be important, when compared with the magnitude of the relative risk associated with passive smoking for diseases such as lung cancer.

(N.B. In this analysis those who had not smoked were classified as passive or never smokers according to whether or not they lived with a smoker.)

It is evident that the conclusion of EPA2 that confounding by other risk factors can be ignored is erroneous.

The study of FONT is considered of high quality by EPA (though see section 3.20 for comments on its weaknesses), and large enough to justify calculating population estimates of risk based on it alone. This study contains detailed data on diet, occupation, personal medical history, and other exposures of interest, but these data were not considered as potential confounding variables in the paper which appeared late in 1991. It would seem to me a relatively quick and easy task to organize a detailed analysis to be done looking at the effect of adjustment for these variables on the ETS/lung cancer relative risk estimate, and that EPA should organize this. (N.B. Care should be taken to take into account the well known fact that adjustment for inaccurately measured variables only partially corrects for the true confounding effect.)

3.11 Specific study weaknesses

Section 5.4.3. considers a range of possible study limitations and sources of uncertainty that might have caused bias in the epidemiological studies. For each potential biasing factor studies are categorized, in Table 5-14, as having or not having the factor, and there is discussion in general terms about whether particular

factors are likely to cause upward bias, downward bias or bias in either direction. At the end of this discussion it is concluded that none of these additional sources of bias "would systematically cause higher observed relative risk estimates". This is a remarkable and totally unjustified conclusion, for two reasons. Firstly, even non-systematic sources of bias, present to a great extent in a small number of studies, can materially affect the overall relative risk estimate. Secondly, and more importantly, EPA2 makes no attempt whatsoever to test, for any potential source of bias, whether the observed relative risk actually tends to differ in those studies classified by them as having it (a cross in Table 5-14A) and those not having it!

In my ETS book I did in fact carry out my own analyses along these lines. Following Breslow and Day (see quotation on pp 5-17 and 18 of EPA2), I felt that the most serious potential sources of bias were those where there was a systematic difference between cases and controls in the circumstances in which the data were collected. As described in section 3.4.6 of my ETS book, I identified ten studies where the general principle of comparing "like with like" had clearly not been adhered to. The median relative risk in these studies (1.74) was substantially higher than in the other studies with no obvious weaknesses in this respect (1.17). This analysis suggests the EPA have underestimated the possibility that weaknesses specific to individual studies may have biassed the overall relative risk estimate.

The individual studies are reviewed in Appendix A of EPA2 with a briefer review given in section 5.4.4., which concentrates on potential biassing factors and on attributing a "tier" (study quality) number to each study. A weakness of the report is that no indication is given as to how the tier number was assigned. Was it purely subjective or was it to some extent semi-quantitative (i.e. assigning plus points for good features and minus points for bad ones)?

Compare chapter 2 of my ETS book with Appendix A of EPA2 for reviews of each individual study.

3.12 Publication bias

In any review or meta-analysis of data from multiple studies it is standard practice to consider formally the possibility that publication bias might have occurred. In my ETS book (p 166) I concluded that some publication bias has occurred, though it appears it can explain only a part of the observed association. This was based on an analysis which demonstrated that the 8 studies (out of 28) showing the highest relative risk estimates were based on significantly ($p<0.05$) lower numbers of lung cancers than those 8 studies showing the lowest estimates. This was consistent with failure to publish results of small studies showing no association. Clearly publication bias is an issue EPA2 should have addressed.

3.13 Failure to consider histological type

EPA2 does not compare and contrast results for different histological types of lung cancer. There are abundant reports that active smoking is much more strongly associated with risk of squamous and small cell cancer than with risk of adenocarcinoma, and if ETS is seen, crudely, as a smaller dose of active smoking (which EPA implicitly assume), it would be expected, if it had any effect at all, to be more strongly associated with risk of squamous and small cell cancer. As discussed in my ETS book (pp 109-111) the data here are in fact conflicting. Though some studies (GARF, PERS, TRIC) produce data seemingly consistent with an association with squamous cell carcinoma, other studies (FONT, LAMT, LAMW and perhaps BROW) seem more consistent with an association with adenocarcinoma, and others who studied data by histological type (KOO, LEE, JANE, KALA) found a similar association, or lack of association, for squamous cell carcinoma as for adenocarcinoma.

The failure to find evidence of a stronger association of ETS with squamous cell carcinoma than with adenocarcinoma is clearly relevant to the discussion of biologic plausibility and the omission to do so is a serious weakness of EPA2.

3.14 The cigarette-equivalent approach

Section 6.3.1 notes that the report uses "the epidemiologic approach because of the abundance of human data from actual environmental exposures" stating that "the assumptions are fewer and more valid than for the cigarette-equivalents approach". However,

the EPA do not list the assumptions behind the two approaches to allow a verification of this statement. In my view, both approaches involve a very considerable number of assumptions and uncertainties indeed, and it would be preferable to present estimates calculated by the EPA using both approaches. This would give better insight into how contingent the estimates are on the approach used.

In fact, though there are obviously differences depending on the details of each approach, it is generally true that the cigarette-equivalents approach tends to produce much lower risk estimates, often by two or three orders of magnitude, than does the epidemiologic approach. While, in sections 6.2.1 and 6.2.2, results of other published risk assessments using both approaches are described, there are no summary paragraphs or tables to make it clear to the reader that the cigarette-equivalents approach does tend to produce much lower estimates. Furthermore, nowhere in the report is it made clear that the amount of particulate matter estimated to be retained in the lung by an average ETS exposed individual is an extremely small proportion (less than 0.1% and perhaps as low as 0.01%) of that retained by an average smoker. Nor is it pointed out that the cotinine based estimate of relative nicotine uptake which is given as 1% (though my review of the evidence suggested 0.5%) is likely to mislead as nicotine in ETS may be absorbed without reaching the lungs. It is also not made clear that in contrast (see my ETS book pp 123 and 124) the overall epidemiological evidence, if unbiassed, suggests that ETS exposure

(from marriage to a smoker) is something like 10-20% of that from active smoking. This 10-20% estimate can also be made from the data given in the final column of Table D-4 of EPA2 but EPA fail to do so.

The sharp conflict between the risks indicated by the cigarette-equivalents approach and those indicated by the epidemiologic approach is of great importance in evaluating the overall evidence since it provides an a priori argument for doubting the validity of the epidemiological data. Not even to make it apparent to the reader that there is such a conflict, and to argue, as EPA does, that only the epidemiologic data should be used, biases the whole report.

3.15 Restriction to US studies

Now that there are data from a relatively large number of US studies I would agree that it is appropriate to restrict attention to US data only, when deriving estimates of risk applicable to the US. In any case, I believe that lack of good data on misclassification in Japanese and other Asian populations would render it virtually impossible to use epidemiologic data from studies in this continent when deriving such estimates.

3.16 Adjustment for background ETS exposure

Three aspects of this adjustment procedure particularly concern me. The first is the possibility that misclassified smokers may severely affect the estimated Z value. As smokers typically have

cotinine values that are more than 100 fold higher than those in nonsmokers, inclusion of only a small proportion of true smokers among self-reported nonsmokers may dramatically increase the mean cotinine and bias estimates of Z. There are two methods of getting round this problem. One is to delete subjects with a cotinine above a given value (perhaps 10% of the average level in smokers) from the calculations. The other is to use medians, which are far less affected by a few aberrant values. I prefer using medians anyway, as the distribution of cotinine values is skewed, but in any case one must not, as EPA2 appear to have done, accept mean values where the misclassified smokers have not been deleted.

My second concern arises from the fact that the cotinine data from which the Z values derive come from younger populations than are relevant for the older subjects in the epidemiological studies. It is apparent that as people get older, and particularly as they retire, they spend more time at home. The Z values derived from some of the population studies may therefore be marked underestimates, with the numbers of deaths due to ETS being overestimated as a result.

My third concern is that the relative risk estimates used in some of the US studies (BUTL 2.01, CORR 1.90, HUMB 1.98) exceed 1.75, and are thus inconsistent with the Z value used to adjust for background. Equation 6-2, on page 6-11, of EPA2 would actually produce negative estimates of risk if this formula were applied to results for a single study. In theory, just as for misclassification

status, adjustment should be study by study but this would not produce valid answers in this case, and it would not do so also if the relative risk were slightly less than Z. (A relative risk of 1.74 when adjusted for background would become over 100!) All this suggests to me that an appropriate adjustment procedure should take into account the variability of both the Z and the relative risk estimate, though at the time of writing I am not in a position to recommend what such a procedure should be.

3.17 Estimation of US female never smoking mortality rates by exposure to ETS

The formulae to derive mortality rates attributable to non tobacco smoke related causes, ever smoking, spousal ETS, and background ETS seem straightforward enough given assumed values of the number in the population, the number of lung cancers, the proportion of ever smokers, the proportion of never smokers exposed to spouse smoking, the relative risks associated with ever smoking and with spouse smoking, and the Z value.

Whether it is appropriate to use American Cancer Society data to estimate relative risks for ever smoking is, however, open to question. This population is of higher than average social status, being virtually all white, and being exposed less to occupational factors, so that their risk from non tobacco smoke related causes would be expected to be atypically low.

Another problem is that no account has been taken of misclassification in estimating the ever smoker/never smoker relative risk. Elsewhere (Lee, 1991), I estimated, that assuming even 1% of ever smokers deny smoking on interview would have the effect of reducing the estimated total number of deaths among never smokers (and therefore the number attributable to ETS) by a factor of as much as 20%.

It is well known that there is substantial misdiagnosis of lung cancer on death certificates. It would be more appropriate to refer to "reported lung cancer deaths" than to "lung cancer deaths" when presenting results.

3.18 Extension of estimates for females to estimates for males

This has already been discussed in section 3.2. As noted there, the decision to ignore data for males, which show no association after adjustment for minimal misclassification, and to use female-derived relative risks to estimate risks for males is inappropriate. Certainly estimates of risk for males derived in this way are subject to extreme uncertainty that is not reflected properly in EPA2.

3.19 Extension of estimates for never smokers to ex-smokers

There is little or no direct epidemiological evidence on risk in relation to ETS exposure for ex-smokers (the study by Varela looked at this but found no effect) or on levels of ETS exposure in

ex-smokers as distinct from never smokers. It is therefore impossible to make any reliable estimate based directly on relevant data. However to assume, as EPA have done, that risk estimates based on results for never smokers are applicable also to ex-smokers who have given up for five years or more seems remarkably simplistic. Might not any effects of ex-smoking and ETS interact? Might not the situation depend on how long ago the smoker gave up, or why? There seems to be no scientific justification whatsoever for extrapolating estimates to ex-smokers. EPA would do better to present as their main conclusions results for never smokers. If they feel they must say something about ex-smokers, estimates should be added only in a statement which makes the assumptions clear and emphasises that the estimates are really only a stab in the dark.

3.20 Use of FONT to derive alternative estimates

It may seem reasonable for EPA to have presented estimates based solely on FONT since it is large, and unusually has cotinine data to allow an internal estimate of the Z-value. It should be realized, however, that despite EPA giving it Tier 1 classification FONT does have some weaknesses:

(i) It is still ongoing and data are incomplete.

(ii) Although extensive data have been collected for dietary and other risk factors no attempt was made to adjust for them in analysis.

(iii) Response rates varied markedly between cases (84%) and controls (72%).

(iv) All population controls were self-respondents whereas next-of-kin responded for 34% of cases.

(v) Analyses presented failed to take into account what might be termed "relevant denominators". Thus the analysis of spousal ETS exposure is not limited to married women, the analysis of ETS from other household members is not adjusted for number of other household members, the analysis of occupational ETS exposure is not limited to working women, etc.

Also the results were somewhat unexpected in that they reported a significant association between spousal exposure and adenocarcinoma, only weakly related to active smoking, and reported no association between spousal exposure and squamous cell carcinoma, strongly associated with active smoking.

These points make it clear that presenting, as EPA does, estimates based on this one study as main conclusions of the report, at the expense of the other 10 US studies, is inadvisable.

EPA2 does not make it clear whether the Z values derived from the cotinine data in the controls from FONT were based on all the subjects, or whether misclassified smokers had been included. If they had not been, the results based on means should be ignored. In any case the results based on medians are to be preferred bearing in mind the skewed nature of the cotinine data.

It should not be forgotten that FONT did not show an RR increase in relation to spouse smoking that was significant at the 95% confidence interval and even when using a 90% confidence interval it was only marginally significant (lower limit 1.01). This implies that whatever estimates of lung cancer deaths attributable to ETS are calculated, they must have a limit of around zero. Nowhere is this made clear. Estimates from FONT are used to compare with estimates derived from 11 US studies to try to get some insight into how much the conclusions depend on the data assumed. Since FONT is one of the US studies, and a major one at that, the two sets of estimates are not independent so the comparison is not valid. It would have been better to compare and contrast estimates based on FONT with those based on the other ten US studies. Since the data excluding FONT are not statistically significant, the reader would at least then have insight into how contingent the overall conclusions are on including data from this study.

3.21 Failure to characterize uncertainties properly

A strong message to the EPA from the SAB following review of EPA1 was to characterize better the uncertainties of the risk estimation procedure. In the conclusions in section 1 of the report it is stated that "an estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate". I submit

that the range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers totally fails to give any idea whatsoever of the true amount of uncertainty about the range.

The values of 2,500 (actually 2,480) and 3,300 come from Table 6-5 which represent point estimates from FONT based on two alternative Z-values, of 2.6 (using median cotinine levels) and 2.0 (using means). However this totally ignores sampling variation which on its own would make the lower limit close to zero whether one used data from FONT or from the combined US studies, since both have lower 90% confidence limits close to 1.00. If 95% confidence limits were used, which I have already argued is more appropriate, the lower limit would reach zero. When one additionally takes into account variation in the assumed value of numerous parameters in the estimation process, such as misclassification rates, frequency of smokers and exposure to ETS, and Z-values, and also takes into account the possibility that various biasing factors, ignored by EPA, actually are important, it is abundantly clear that the estimated range is hugely underestimated. The variability does not exclude the possibility, for example, that the number of deaths among never smokers attributable to ETS might not be anything like 2,000. The number might be 12 as estimated by Arundel et al (see p 6-8 of EPA2), and it certainly might be zero.

3.22 Inherent bias due to data-derived decisions

It is a well recognized principle that procedures for analysis of data should be defined in advance to avoid the possibility of

bias resulting from over- or under-emphasis of specific data which happen to fit in or not to fit in with preconceived ideas of the underlying truth. EPA have not done this. Classification of studies as of different quality should have been conducted by an independent team who did not know what the results of the studies were, but this has not happened. One gets the very strong impression that WUWI was given specific attention, and criticisms of it found, simply because it happened to show a significant negative relationship of ETS with lung cancer. The decision to concentrate on FONT seems also to have depended, not only on the fact that it was considered large and relatively well conducted, but also on the fact that it came up with a relative risk that was positive enough for EPA to arrive at a large estimate of numbers of deaths. One must ask oneself whether EPA would have acted the way it did had FONT produced a much lower relative risk estimate.

Even where principles have been defined in one part of the report, they have not been kept to in other parts of the report, apparently because the data do not fit in with the message they wish to put over. Thus the principle that estimates should be based on data relevant to the situation is used to justify restricting attention to US data. However, when the data, limited as it is, for males and for ex-smokers shows no association of ETS with lung cancer, this principle is suddenly dropped and female data for never smokers, which do happen to show an association (and then only with spousal and not with workplace or childhood ETS exposure), are used to provide estimates.

4. Hazard Identification I: Lung Cancer in Active Smokers, Long-term Animal Bioassays, and Genotoxicity Studies

EPA2, on page 4-1, argue that, because of the dose-related association between lung cancer and tobacco smoking, it is "reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers". Later, on page 4-9, they state that the results "clearly establish the plausibility that ETS is also a human lung carcinogen" and affirm that "ETS exposure is a public health concern". Were this the overall thrust of the chapter, I would not disagree - the results cited do suggest a need to evaluate the possibility that ETS might cause lung cancer. It is when EPA2 switches tack and concludes that ETS can be classified, in the absence of epidemiological data on ETS, as a group A carcinogen that one must take issue.

In the first place it is not made clear that all the relevant components of the argument put forward in chapter 4 (that the epidemiology of active smoking shows a strong, dose-related association with lung cancer, that ETS contains many animal carcinogens present in mainstream smoke, and that nonsmokers are exposed to these carcinogens) could have been made many years ago, but that the scientific world at large did not start to express any need for action until after Hirayama and Trichopoulos published their early epidemiological results on ETS in 1981. Indeed, if the argument in chapter 4 is correct, one must inevitably wonder what a

regulatory body such as EPA were doing sitting on these results for so long, when they could have classified ETS as a carcinogen 20 years ago.

The truth of course is that, though the data cited in this chapter generate a hypothesis to be tested, they do not of themselves prove that ETS causes lung cancer. There are a number of reasons for this:

(i) There may be chemical similarities between ETS and mainstream smoke but the substances are not the same. In the absence of any data demonstrating which chemicals or combinations of chemicals lead to the association of active smoking with lung cancer, one cannot be certain that relevant exposure occurs.

(ii) The claim that there is no threshold for active smoking, even if true, does not mean that one might not exist for ETS, even if ETS and mainstream smoke are essentially similar. There are obviously difficulties in choosing an appropriate smoke constituent for extrapolation. However it is certainly relevant to note that lung cancer in active smokers frequently has been assumed to arise because of deposition of particulate matter in the lung, and that the amount of particulate matter retained in the lung from ETS, is very much less (by a factor of 1,000 or even 10,000) than that retained from mainstream smoke. Clearly exposure from ETS might be below a threshold.

(iii) The data for active smoking have anyway not been properly examined to see whether a threshold does occur. The lowest groups in the prospective studies in Table 4-3 are in all

cases broad, often include 10-a-day smokers, and always include 5-a-day smokers. No analyses have been conducted for 1-a-day or 2-a-day smokers to test whether any increase in risk is evident. (N.B. Such analyses should take care to consider the possibility that heavy smokers might misrepresent the amount they smoke.)

Other criticisms of the material presented in section 4 are as follows:

(i) In section 4.2.1 time trends in overall cigarette consumption are compared with time trends in overall lung cancer mortality rates. This is invalid because of the strong association reported between duration of smoking and lung cancer mortality. Overall lung cancer rates may be increasing at a time when there are clear declines in rates at younger ages, and it is absolutely necessary that trends be compared on a cohort basis for any meaningful conclusion to be drawn.

(ii) In section 4.2.3 it is stated that the "gradient for adenocarcinomas .... is shallower than the slopes for other types [of lung cancer]". This understates the dramatic difference, and the very weak association of active smoking with adenocarcinoma. This is important as it should, but does not, lead in to the point that the relationship reported between ETS and adenocarcinoma in some studies is similar in magnitude to that reported between active smoking and lung

cancer, which is difficult to interpret (inter alia because active smokers surely get much more ETS exposure than exposed nonsmokers).

(iii) The section, 4.3.1, on inhalation studies is inadequate. For balance it must be mentioned that rat and mouse inhalation studies have either produced no excess of lung cancers in the exposed groups or have produced at best equivocal results.

5. Other points

On page 1-7 it is stated that "for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these [Japanese and Greek] societies than in Western countries, where other sources of ETS exposure are generally higher". This is unsupported speculation and could well be untrue. In Japan, for example, many men spend little time at home and many women work.

On page 3-6 it is incorrectly stated that nicotine is specific to tobacco. Not so; it has been detected in tomatoes, aubergines, peppers and other solanaceous vegetables, and in tea, conceivably in large enough quantities to interfere somewhat with quantification of ETS exposure.

On page 3-16 it is noted that "the cigarette equivalent dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much as 4-aminobiphenyl". Not to note here that a passive smoker is likely only to retain 0.01-0.1% as much particulate matter as an active smoker imparts a huge bias to the whole conclusion regarding cigarette equivalents.

6. Conclusions

1. The arguments put forward by EPA in section 4, which could equally well have been made 20 years ago, merely generate a hypothesis to be tested and do not of themselves justify classification of ETS as a group A carcinogen. ETS and mainstream smoke are not the same, exposure to many chemicals is orders of magnitude lower from ETS, and evidence from active smoking does not demonstrate absence of a threshold dose.

2. The epidemiological evidence also does not justify classification of ETS as a group A carcinogen. The evidence relating risk of lung cancer to spouse smoking in females does not provide convincing evidence that ETS causes lung cancer. The second draft of the EPA report has a number of major deficiencies.

   a) It totally underestimates the various possibilities of bias. Misclassification of smoking status is inadequately correlated for by an obscurely presented procedure, which is mathematically incorrect, involves numerous dubious assumptions, and ignores relevant data indicating a higher misclassification rate than that employed by EPA. The conclusions that confounding by other risk factors does not cause bias ignores extensive evidence which indicates it does. Specific study weaknesses are noted, but no attempt is made to quantify the resulting bias. The possibility of publication bias is not even mentioned.

b) Evidence not readily fitting in with the hypothesis that ETS causes lung cancer is ignored or given little weight, while evidence that does fit in is overemphasised. The evidence that ETS is not associated with lung cancer risk in males or in ex-smokers is given little weight, and it is not even mentioned that in female never smokers lung cancer risk is not associated with workplace or childhood ETS exposure. Instead risk estimates derived from spouse smoking in female never smokers are assumed to apply to males, to ex-smokers, and to other sources of ETS exposure. 90% confidence limits are used, instead of the standard 95% limits, in an attempt to make even the spousal data statistically significant. The implausibility of some of the epidemiological findings, bearing in mind the much lower exposure to smoke constituents from ETS than from mainstream smoke, and the fact that some studies claim an effect for a type of lung cancer scarcely associated with active smoking, is not made clear.

c) The uncertainties are not at all adequately characterized. The range of lung cancer deaths attributable to ETS in the US is estimated to be between 2,500 and 3,300, implying considerable precision. This estimated range fails even to take into account sampling variation, which of itself would reduce the lower limit to about zero. It also fails

to account for variation resulting from uncertainty in the various parameter values used and assumptions made in the estimation process.

There are also a number of other deficiencies of the report, as discussed in these comments.

When commenting on the first draft of this report I concluded that it was substantially flawed, and should be throughly reconsidered. Detailed examination of the second draft leads only to the same conclusion.

7. References

References are only given for papers not already cited in EPA2.

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Lee, P.N. (1991) Weaknesses in recent risk assessments of environmental tobacco smoke. Environmental Technology, 12, 193-208.

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TABLE 1

Comparison of claimed effects of smoking habit misclassification using my method and that of Wells and Stewart (US studies)

	Wells and Stewart[1]			Lee[2]		
	Active	Passive risk		Active	Passive risk	
Study	Risk	Unadjusted	Adjusted	Risk	Unadjusted	Adjusted
BROW	4.30	1.52	1.50	4.30	1.82	1.76
BUFF	7.06	0.81	0.70	7.06	0.80	0.69
BUTL(Coh)	4.0	2.02	2.01	-	-	-
CORR	12.40	2.07	1.90	9.47	2.07	1.63
FONT	8.0	1.29	1.26	8.01	1.32	1.17
GARF	*	1.31	1.24	8.01	1.23	1.09
GARF(Coh)	3.5	1.17	1.15	8.01	1.17	1.02
HUMB	16.3	2.20	1.98	16.27	2.34	1.95
JANE	8.0	0.86	0.78	8.01	0.75	0.65
KABA	5.90	0.79	0.74	8.01	0.79	0.68
Kabat(1990)	-	-	-	8.01	0.90	0.79
WU	4.38	1.41	1.31	2.95	1.20	1.14
Meta-analysis (fixed effects)						
Relative risk		1.22	1.17[3]		1.18	1.04
90% confidence limits		1.09-1.37	1.02-1.34		1.04-1.34	0.91-1.18
95% confidence limits		1.07-1.40	1.00-1.37		1.02-1.37	0.89-1.21

1 Taken from EPA2

2 All source data included are fully documented in my ETS book. The method of adjustment is described in my paper "Correcting meta-analysis.." (29.11.91). An observed concordance ratio (ever/never smoking) of 3.0, a misclassification rate of 2% of ever smokers as never smokers and a multiplicative model of passive and active risk are assumed.

3 Table 5-8 gives 1.19 (1.04-1.35) but this is inconsistent with the data cited for the individual studies

TABLE 2

Percentage reduction in relative risk due to misclassification as estimated by Wells and Stewart and as estimated using my method, with a 1% misclassification rate, and EPA estimates of active smoking risk

Study	Wells and Stewart	Lee
BROW	1,3%	1.6%
BUFF	13.6%	6.3%
CORR	8.2%	9.2%
FONT	2.3%	4.5%
GARF	5.3%	5.7%
GARF(Coh)	1.7%	1.7%
HUMB	10.0%	8.1%
JANE	9.3%	5.3%
KABA	6.3%	3.8%
WU	7.1%	4.2%

TABLE 3

Percentages of self-reported non-smokers with cotinine levels consistent with smoking

Study	Wells and Stewart Table B3(females)	Lee Table 3.34	Sex
Coultas	4.9% (23/466)	5.7% (51/896)	M+F
Cummings	0.8% (3/368)	0.9% (6/669)	M+F
Dickinson	-	2.8% (10/355)	M+F
Haddow 86	1.3% (3/232)	1.3% (3/232)	F
Haddow 88	0.9% (13/1508)	-	F
Haddow 87	-	3.9% (112/2871)	F
Heller	-	2.7% (62/2292)	M+F
Lee	2.2% (10/458)	2.5% (20/808)	M+F
Perez-Stable	-	6.6% (13/196)	M+F
Pierce	6.1% (19/311)	5.0% (31/622)	M+F
Riboli	0.5% (4/756)	3.4% (47/1369)	F
Slattery 1	-	6.4% (7/109)	M
Slattery 2	-	2.1% (8/379)	F
Slattery 3	-	17.2% (27/157)	M
Wagenknecht	-	4.2% (145/3445)	M+F
Wald 84	-	0.9% (2/221)	M
Wald 90	-	1.1% (2/184)	M+F
Total	1.8% (75/4099)	3.7% (546/14805)	

Annex A

Detailed comments on the Wells-Stewart methodology for correcting for smoking habit misclassification

1. Introduction

Appendix B, which describes the Wells-Stewart method, is remarkably obscurely written and the various assumptions behind it are not clearly expressed. It is very difficult for the interested reader to know what Wells has done, let alone to try to evaluate its correctness. In this Annex, therefore, it is necessary to first (in section 2) describe the method and list the assumptions, before (in section 3) evaluating it for possible weaknesses.

2. The method

Unlike in EPA1, correction has been made for smoker misclassification on a study-by-study basis. Below the method used is described using, as does Appendix B, the Correa study data for females as an example.

2.1 Input data from the Correa study

The data used that are specific to the Correa study are as follows (see page 13-11)

Proportion of control wives who have never smoked = 52.8%
Proportion of control never smoking wives whose husbands smoked = 45.9%
Relative risk of lung cancer for current smokers compared to never smokers = 10.0
Relative risk of lung cancer, among never smoking wives, for those whose husbands smoked compared to those whose husband did not smoke = 2.07.

These relative risks are unadjusted for smoking habit misclassification.

2.2 Generating the full distribution of observed smoking prevalence among the controls

A first major step involves estimating the elements of the following table giving the distribution of the control women by their own and by their husband's smoking status.

Husbands' smoking status	Wives' Own Smoking Status				
	Never	Former	Occasional	Regular	Total
Never					
Ever					
Total					1.000

The bottom left hand element of this data is the proportion of wives reporting never having smoked and an estimate, 0.528, is provided directly by the Correa study. Multiplying this by 0.459, the proportion of control never smoking wives whose husbands smoked - also provided directly by the Correa study - gives 0.242, and subtracting this from 0.528 gives 0.286, the proportion of control never smoking wives whose husbands never smoked. Thus using data that are available from the Correa study allows us to fill in only the following elements.

Husbands' smoking status	Wives' Own Smoking Status				
	Never	Former	Occasional	Regular	Total
Never	0.286				
Ever	0.242				
Total	0.528				1.000

To fill in the remainder of the table requires a number of assumptions:

Assumption A: 35.5% of ever smokers are former smokers.

Assumption B: 90% of current smokers are regular smokers.

Assumption C: There is a concordance factor of 2.8 for wives (ever/never smokers) versus husbands (ever/never smokers).

Assumption D: There is a concordance factor of 2.2 for wives (former/never smokers) versus husbands (~~ever~~ former/never smokers).

By subtraction, a proportion 0.472 = 1 - 0.528 of the wives have ever smoked. Under Assumption A 0.355 x 0.472 = 0.167 are ex-smokers. (Actually, the product is 0.168. Here, and subsequently I will ignore problems which may result from rounding error - EPA may have used initial data to more than 3 significant figures initially). Subtracting 0.167 from 0.472 gives us 0.305 current smokers. Using Assumption B this may be split into 0.275 regular and 0.030 occasional smokers.

We now have

Husbands' smoking status	Wives' Own Smoking Status				
	Never	Former	Occasional	Regular	Total
Never	0.286				
Ever	0.242				
Total	0.528	0.167	0.030	0.275	1.000

Now consider the 2 x 2 table

Husbands' smoking status	Wives' status	
	Never	Former
Never	0.286	0.167 - x
Ever	0.242	x

Under assumption D the concordance factor or cross-product ratio (0.286)(x)/(0.242)(0.167-x) = 2.2 This solves directly to give x = 0.109 and 0.167 - x = 0.058.

Similarly if we consider the 2 x 2 table

Husbands' smoking status	Wives' status	
	Never	Ever
Never	0.286	0.472 - y
Ever	0.242	y

Under assumption C, the cross-product ratio (0.286)(y)/(0.242)(0.472-y) = 2.8. This solves directly to give y = 0.332 and 0.472 - y = 0.140.

Adding across columns, 0.286 + 0.140 = 0.426, and 0.242 + 0.332 = 0.574. Thus the overall table so far is

Husbands' smoking status	Wives' Own Smoking Status Never	Former	Occasional	Regular	Total
Never	0.286	0.058			0.426
Ever	0.242	0.109			0.574
Total	0.528	0.528	0.030	0.275	1.000

Subtracting across columns shows us that there are 0.426 - 0.286 - 0.058 = 0.082 current smoking (occasional + regular) wives married to never smokers, and 0.574 - 0.242 - 0.109 = 0.223 current smoking wives married to ever smokers. Splitting these 90:10 into regular:occasional, under assumption B, allows the complete table to be generated.

Husbands' smoking status	Wives' Own Smoking Status Never	Former	Occasional	Regular	Total
Never	0.286	0.058	0.008	0.074	0.426
Ever	0.242	0.109	0.022	0.201	0.574
Total	0.528	0.167	0.030	0.275	1.000

This is Table B-10 of Appendix B. Note there is an additional assumption implicit in the final step.

Assumption E: The concordance factor for occasional versus never smoking wives is equal to that for regular versus never smoking wives.

2.3 Generating the full distribution of relative risks

The next major step involves estimating the components of the following table of risks relative to all never smokers.

Husbands' smoking status	Wives' own smoking status: Never	Former	Occasional	Regular
Never				
Ever				
Weighted average	1.00			

From Table B-10 we know the relative frequency of never smoking wives by husbands' smoking status - ever:never = 0.242:0.286. The risks reported from the Correa data are in the ratio 2.07:1. It then follows that the risks, relative to all never smokers, are given by 2.07r and r where r is the solution to the equation $0.286r + 0.242 \times 2.07r = 0.528$. This gives $r = 0.67$ and $2.07r = 1.39$. Thus we have so far

Husbands' smoking status	Wives' own smoking status: Never	Former	Occasional	Regular
Never	0.67			
Ever	1.39			
Weighted average	1.00			

The Correa data report that current smokers have 10 times the risk of lung cancer of never smokers. If we make two further assumptions:

Assumption F: Current regular smokers have the same risk as current smokers, and

Assumption G: Husband's smoking status does not affect the risk of lung cancer among current smokers.

we can at once fill in further elements to give

Husbands' smoking status	Wives' own smoking status: Never	Former	Occasional	Regular
Never	0.67			10.00
Ever	1.39			10.00
Weighted average	1.00			10.00

If we now make the further assumption

H. That occasional smokers have 20% of the excess risk of lung cancer of that of regular smokers,

we can calculate relative risks of 0.2(10-1) + 1 = 2.80. We now have

Husbands' smoking status	Wives' own smoking status: Never	Former	Occasional	Regular
Never	0.67		2.80	10.00
Ever	1.39		2.80	10.00
Weighted average	1.00		2.80	10.00

To complete the table we require 2 further assumptions:

Assumption I: The relative risk for husbands' smoking is the same for former smokers as it is for never smokers (i.e. 2.07).

Assumption J: Misclassified former smokers have 9% of the excess risk of lung cancer of that of regular smokers.

Assumption J allows us to calculate a weighted average of 0.09(10-1) + 1 = 1.81. From Table B-10 we know the relative frequency of former smoking wives by husbands smoking status - never:ever = 0.058:0.109. From the Correa data the risks are in the ratio 1:2.07. It then follows that the risks, relative to all never smokers, are given by 2.07s and s where s is the solution to the equation

$0.058s + 0.109 \times 2.07s = 0.167 \times 1.81.$

This gives s = 1.07 and 2.07s = 2.21. We now have the completed table

Husbands' smoking status	Wives' own smoking status: Never	Former	Occasional	Regular
Never	0.67	1.07	2.80	10.00
Ever	1.39	2.21	2.80	10.00
Weighted average	1.00	1.81	2.80	10.00

This is Table B-11 of Appendix B.

2.4 Generating the full distribution of observed smoking prevalence among the cases

If we now multiply the distribution of controls (Table B-10) by relative risks (Table B-11) we get

Husbands' smoking status	Wives' Own Smoking Status: Never	Former	Occasional	Regular	Total
Never	0.192	0.062	0.022	0.740	1.016
Ever	0.336	0.241	0.062	2.010	2.649
Total	0.528	0.303	0.084	2.750	3.665

This, Table B-12 of Appendix B, is the relative frequency of the cases in the different cells. Dividing the entries by 3.665 gives the absolute frequencies:

Husbands' smoking status	Wives' Own Smoking Status: Never	Former	Occasional	Regular	Total
Never	0.052	0.017	0.006	0.202	0.277
Ever	0.092	0.066	0.017	0.549	0.723
Total	0.144	0.083	0.023	0.751	1.000

This is Table B-13 of Appendix B.

2.5 Applying the misclassification rates

The next stage is to complete a table of wives' true smoking status against wives' observed smoking status. From Table B-10 (see section 2.2 above) the marginal totals for wives' observed smoking status are available directly. Assuming also:

Assumption K: No never smokers are misclassified as ever smokers

Assumption L: No former smokers are misclassified as current smokers

Assumption M: Current smokers are not misclassified between occasional and regular smokers

one can start with:

Wives' Observed smoking status	Wives' True Smoking Status Never	Former	Occasional	Regular	Total
Never	a	b	c	d	0.528
Former	0	e	f	g	0.167
Occasional	0	0	0.030	0	0.030
Regular	0	0	0	0.275	0.275
Total	a	b+e	c+f+0.030	d+g+0.275	1.000

where a, b..g are 7 elements of the table still to be estimated. Five further assumptions are used:

Assumption N: A proportion 0.0100 of true current regular smokers are misclassified as never smokers (from Table B-3)

Assumption O: A proportion 0.1510 of true current occasional smokers are misclassified as never smokers (from Table B-3)

Assumption P: A proportion 0.0107 of true regular smokers are misclassified as former smokers (from Table B-3)

Assumption Q: A proportion 0.0800 of true occasional smokers are misclassified as former smokers (from Table B-3)

Assumption R: A proportion 0.1081 of true former smokers are misclassified as never smokers (from Table B-4)

Assumptions N and P yield two equations in d and g:

$$d = 0.0100\ (d + g + 0.275)$$

$$g = 0.0107\ (d + g + 0.275)$$

which gives $d = 0.00281$, $g = 0.00301$.

Assumptions O and Q yield two equations in c and f:

$$c = 0.1510\ (c + f + 0.030)$$

$$f = 0.0800\ (c + f + 0.030)$$

which gives $c = 0.00590$, $f = 0.00315$.

From the row total for ex-smokers, we then get

$$e = 0.167 - 0.00315 - 0.00301 = 0.16084$$

Assumption R gives

$$b = 0.1081\ (b + e)$$

so that, as e is known, we derive b = 0.01953.

Finally, from the row total for never smokers, we get

$$a = 0.528 - 0.01953 - 0.00590 - 0.00281 = 0.49976$$

The full table is therefore:

Wives' Observed smoking status	Wives' True Smoking Status: Never	Former	Occasional	Regular	Total
Never	0.49976	0.01953	0.00590	0.00281	0.528
Former	0	0.16084	0.00315	0.00301	0.167
Occasional	0	0	0.03000	0	0.030
Regular	0	0	0	0.27500	0.275
Total	0.49976	0.18037	0.03905	0.28082	1.000

This is a more precise version of Table B-14 made available by EPA in December 1991.

From this table three ratios are calculated from the never raw and the total column:

$R_1 = 0.01953/0.167 = 0.11692$ (former)

$R_2 = 0.00590/0.030 = 0.19672$ (occasional)

$R_3 = 0.00281/0.275 = 0.01020$ (regular)

These ratios are then applied to the rows of Tables B-10 and B-11 as follows:

Controls/Husband Never (Table B-10) : Corrected never smokers = $0.286 - 0.058R_1 - 0.008R_2 - 0.074R_3 = 0.27690$

Controls/Husband Ever (Table B-10) : Corrected never smokers = $0.242 - 0.109R_1 - 0.022R_2 - 0.201R_3 = 0.22308$

Controls/Husband Ever (Table B-13) : Corrected never smokers = 0.05229 - $0.017R_1$ - $0.006R_2$ - $0.202R_3$ = 0.04705

Controls/Husband Ever (Table B-13) : Corrected never smokers = 0.09178 - $0.066R_1$ - $0.017R_2$ - $0.549R_3$ = 0.07519

This is equivalent to what is given in Table B-15 of Appendix B.

Finally, the corrected risk imputed to ETS is obtained by taking the cross product ratio from the four corrected never smoker values above:

Corrected risk = (0.27690 x 0.07519)/(0.22308 x 0.04705)

= 1.984

The bias is thus true risk/corrected risk = 2.07/1.984 = 1.044

3. Detailed comments on the method and assumptions

Correction for smoker misclassification on a study-by-study basis is certainly a far preferable approach to a single correction to the overall meta-analysis relative risks. There are however a number of detailed points that need to be made.

3.1 Generating the control data

The actual technique for generating the control data given the various assumptions made is straightforward enough. The questions of real interest relate to the appropriateness of the various assumptions used.

Assumption A, that 35.5% of ever smokers are former smokers is based on data from 9 studies in the UK, US and Sweden shown in Table B-16 of Appendix B. It is somewhat surprising that no attempt has been made to study available survey data for many countries on this issue, and that no mention is made of the fact that this percentage is likely to be strongly age-dependent. Thus, using national data for the UK published in "UK Smoking Statistics" (Wald et al, 1988, Oxford University Press) we have the following data for 1985 for women showing

a marked increase in the % with age.

		Age			
		25-34	35-49	50-64	65+
(1)	% never smoked	46	45	42	56
(2)	% ever smoked	54	55	58	44
(3)	% ex-smokers	12	17	21	25
(4)	(3) as % of (2)	22.2	30.9	36.2	56.8

Assumption B, that 90% of current smokers are regular smokers, based on the observation that 10% of self-reported current smokers have cotinine values less than 30% of average smoker's levels is of course rather arbitrary, though supported by some data in Table B-1 of Appendix B. While it seems reasonably clear that cotinine values above a certain point are very unlikely to be achievable in the absence of smoking, there is a relatively poor correlation within smokers between self-reported number of cigarettes smoked and cotinine levels, and this may be due to differences in metabolism and manner of smoking as well as to inaccuracies in statements about number smoked. In the absence of data correlating cotinine to risk of lung cancer, one is speculating when one uses cotinine level in smokers to define a low risk group. However the general idea that there is a subset of smokers who have low cotinines, low lung cancer risks and who are particularly likely to report non-smoking is a plausible one and is very similar to assumptions I used some 5 years ago Lee (1987b), and the frequency of this subset assumed by EPA (10%) is not dissimilar from the 6.9% I reported then.

Numerous studies have demonstrated that smokers tend to marry smokers more than expected by chance. In my ETS book, I presented data on the extent of this smoking habit concordance. These data, though rather variable, suggest a rather higher degree of concordance than Assumptions C and D indicate. In particular numerous studies show

concordance ratios in excess of 4 for current smoking. Since the degree of bias is essentially directly proportional to the extent of concordance assumed, it is important that, at a minimum, the EPA present some results showing variation in bias by extent of concordance assumed, making it clear that concordance ratios substantially higher than those assumed are not only plausible, but have been reported in a number of studies.

It should also be realised that Assumption E, that the concordance factor for occasional smokers versus never smokers is equal to that for regular versus never smokers is extremely dubious. In my own large representative UK study Lee (1987b, 1988) I found that the chance of having a spouse who was a manufactured cigarette smoker increased with the reported number of cigarettes a day smoked by the subject. This is inconsistent with assumption E and failure to take this into account will lead to some underestimation of the misclassification bias.

3.2 Estimating the observed relative risks

I find it wrong that one should use Correa's data to estimate a relative risk of 10.0 for current smoking and then (Assumption F) apply the figure of 10.0 to regular smokers. Current smokers include occasional and regular smokers and one should take this into account. In this case, this would increase the relative risk from 10.0 to 10.78 for regular smoking and from 2.80 to 2.96 for occasional smoking, adding almost 10% to the estimated misclassification bias.

I find it quite remarkable that the EPA should assume (Assumption G) that exposure to husbands' smoking should increase the risk of lung cancer for never and former smokers (and to the same extent - Assumption I), but that it should not increase the risk of lung cancer

for current smokers. Were observed increases in risk in relation to husbands' smoking very much less than those in relation to active smoking, it might seem reasonable to assume the risks attributable to exposure from husbands' smoking are negligible in relation to those attributable to active smoking and can therefore be ignored with little inaccuracy. However, when the evidence from a number of studies is highly inconsistent with this view (see Table D-4 of EPA2) this seems unjustified. It seems in any case remarkable to assume risk to active smokers attributable to husbands' smoking when the risks for husbands' smoking and former smokers are assumed to be multiplicative. It would seem to me far more appropriate to assume an increase in risk attributable to husbands' smoking in all subgroups, and to compare and contrast effects on bias estimation of using a multiplicative model and an additive model. (This latter would be more appropriate if ETS were viewed as an additional "dose" of the same exposure, the former would be more appropriate if ETS and active smoking were assumed to act by totally different mechanisms.)

Another problem with the estimation procedure is that the multiplicative model for the effects of husbands' smoking and of former smoking is applied to observed data. There is no logic in this. The multiplicative model will apply (if at all) to the true risks, not the observed risks.

The idea that current occasional smokers have 20% of the excess risk of current regular smokers (Assumption H) is not implausible. In my Human Toxicology paper I estimated 16.7% based on relative cotinine levels of the two groups.

Another problem with this part of the estimation procedure is the treatment of ex-smokers. Though the evidence is indeed reasonably

clear that those ex-smokers who report never having smoked are much more likely than normal to have smoked relatively little and a long time ago (Assumption J), account of this is taken in the wrong stage of the calculations. In order to get the correct distribution of cases by smoking group, it is necessary to apply the correct risks for each group considered. One cannot on the one hand say 35.5% of ever smokers are ex-smokers (which clearly includes short and long term ex-smokers) and then apply risks relevant only to long term ex-smokers to the whole of this group in order to estimate case distributions.

3.3 Generating the full distribution of observed smoking prevalence among the cases

Given the distribution of observed smoking prevalence among the controls and given the corresponding observed relative risks, it is indeed correct to multiply the two together to get the relative observed smoking prevalence among the cases. As noted in the previous paragraph, however, the incorrect treatment of ex-smokers means that Table B-13 is not in any sense a valid estimator of the prevalence of cases by smoking status.

3.4 Applying the misclassification rates

Assumptions K, L and M are generally in line with the idea that those who have smoked are more likely to understate than overstate their smoking history and that, even if some do overstate, this causes much less bias. Thus one does not consider the possibility that never smokers claim to be ever smokers, that former smokers claim to be current smokers or that occasional smokers claim to be regular smokers. This is reasonable. However, I do not see, however, why it is assumed that no regular smokers claim to be occasional smokers.

Assumptions N, O, P, Q and R relate to the various misclassification rates assumed. The most important contributor to bias is the proportion of current regular smokers misclassified as never smokers and in the main body of my comments on EPA2 I note that the proportion assumed by Wells, 0.01, is about half that indicated by the more extensive data available in my ETS book. I do not propose to comment here on the other misclassification rates assumed by Wells, other than to note that my ETS book gives considerable material here that has not been considered, and that it indicates considerable between-study variability that has not been taken into account at any stage by Wells or by EPA2. There is no indication as to how the extent of correction depends on the assumptions made - misclassification rates might, for example, be very much higher in Japan than in Western populations but such a possibility is not formally taken into account.

A final, and important point, is that there is a clear error in the way that the corrected numbers of never smokers are calculated from the material in Tables B-14, B-10 and B-11. This is illustrated below.

Let, for a given population, the true number of never, former, occasional and regular smokers be N, F, O and R respectively. Let their observed numbers be indicated by an asterisk. Using the notation of Table B-7 and noting that various of the P values there are assumed to be zero, we have the following equations.

(1) $N^* = N + F(P_{10}/P_{1.}) + O(P_{20}/P_{2.}) + R(P_{30}/P_{3.})$

(2) $F^* = F(P_{11}/P_{1.}) + O(P_{21}/P_{2.}) + R(P_{31}/P_{3.})$

(3) $O^* = O(P_{22}/P_{2.})$

(4) $R^* = R(P_{33}/P_{3.})$

Substituting from (3) and (4) into (1) and (2) gives

(5) $N^* = N + F(P_{10}/P_{1.}) + O^*(P_{20}/P_{22}) + R^*(P_{30}/P_{33})$

(6) $F^* = F(P_{11}/P_{1.}) + O^*(P_{21}/P_{22}) + R^*(P_{31}/P_{33})$

(6) gives us F in terms of F*, O* and R*, and substituting into (5) gives us what we want, an expression for N in terms of the observed smoking distribution and the P values. Writing $Q = P_{10}/P_{11}$, this is

$$N = N^* - F^*Q - O^*(P_{20}/P_{22} - QP_{21}/P_{22}) - R^*(P_{30}/P_{33} - QP_{31}/P_{33})$$

This is <u>not</u> the same as the formula used by Wells, which is

$$N = N^* = F^*(P_{10}/P_{.1}) - O^*(P_{20}/P_{.2}) - R^*(P_{30}/P_{.3})$$

4. <u>A better methodology</u>

The statistical method for smoking habit misclassification adjustment depends on a whole host of inadequately explained and justified assumptions and imprecisely known parameters. Furthermore, there are a number of clear errors in the method. Thus,

(i) It has been assumed, totally implausibly, that risk from exposure to husbands' smoking multiplies the risk associated with former smoking, but has no effect whatsoever on the risk associated with current smoking.

(ii) The multiplicative model in relation to ETS and to former smoking has been applied to <u>observed</u> risk when it would only apply (if it were appropriate) to <u>true</u> risks, i.e. risks before misclassification.

(iii) The estimated relative risk of current (versus never) smoking has been applied in the procedure to current <u>regular</u> smoking. Current smokers include both regular and occasional smokers.

(iv) In estimating the observed smoking habit distribution of the cases, the frequency of all former smokers (long-term and short-term) has been multiplied by a risk factor derived for long-term smokers only.

(v) The actual method of estimating the numbers of never smokers corrected for misclassification, given the observed distribution of cases and controls by self and spouse's smoking habits and given the assumed misclassification rates, is mathematically erroneous.

A better methodology is clearly needed. The method I described in my document of November 1991 is simple, exact, involves fewer assumptions, and is clearly explained. It only deals with misclassification of ever as never smokers, but there may be advantages to that in a number of ways. Extension of it to more smoking groups is in fact not difficult and I can provide details if this is required.

ANNEX B

DIFFERENCES BETWEEN ACTIVE SMOKERS, EX-SMOKERS, THOSE EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE, AND THOSE NOT EXPOSED TO TOBACCO SMOKE

by

A.J. Thornton and P.N. Lee

Date: 23rd June 1992

1. Introduction

This report concerns the extent to which smokers and non-smokers, or individuals exposed or non-exposed to environmental tobacco smoke, differ in the frequency with which they are exposed to various risk factors which may affect the incidence of certain diseases. Our analyses are based on a database collected by the Health Promotion Research Trust, from a survey of 9003 people, aged 18+, from England, Scotland and Wales. The survey took place in 1984-1985, and was conducted in three stages. The first stage was a questionnaire completed during an interview at the subject's home. The second stage consisted of a visit by a nurse approximately one week after the date of the first interview, during which physiological measurements and simple tests of cognitive function were carried out. The third stage of the survey took the form of a self-completion questionnaire, designed to assess personality and psychiatric status, which was left at the respondent's house by the nurse.

At the first interview, information was collected on a wide range of factors, covering aspects of self-reported health, health attitudes and beliefs, dietary habits, leisure, work and exercise, smoking habits, and alcohol consumption, and the subjects were also asked about their home and family circumstances, education and income. During the home visit by the nurse, measurements of height, weight, girth, blood pressure, pulse rate, respiratory function, and environmental and exhaled carbon monoxide

were made, and tests of reaction time, memory and reasoning were also carried out. The self-completion questionnaire used three measures of personality; namely Type A personality, neuroticism and extroversion; and psychiatric status was assessed using the General Health Questionnaire. Nine hundred variables per case were collected by the interview questionnaire, 87 variables at the measurement stage of the survey, and 96 variables by the self-completion questionnaire.

So that differences in exposure to the various risk factors in individuals exposed to different amounts of tobacco smoke could be seen, the respondents were classified into one of four groups, depending on their smoking habits. Never smokers were made up of people who did not smoke themselves, and who lived in households where none of the occupants smoked. Passive smokers were classified as those who did not actively smoke themselves, but who lived with somebody who did, and were therefore potentially exposed to environmental tobacco smoke. Those who had smoked at least one cigarette per day for a minimum of six months but no longer did so, or who had ever smoked cigars or a pipe but had given up, were grouped as ex-smokers, while current smokers consisted of those people who were currently smoking at least one cigarette per day, or who currently smoked cigars or a pipe. Respondents who smoked cigarettes, but at a rate of less than one per day were also classified as current smokers, while those who had only tried to smoke a cigar or pipe once or twice were placed in one of the other three exposure groups, depending on their exposure to other sources of tobacco smoke.

Percentages of those exposed to each of the risk factors were computed for the four smoking groups. The percentages were standardised, by the direct method, to the overall age distribution of the population under study using six groups (18-29, 30-39, 40-49, 50-59, 60-69, 70+) and are presented as %A in the tables. Differences in amount of exposure from that in the never smoking group were tested for significance by rank tests, stratified for age, using the method of Fry and Lee (1988). Probability values (two-tailed) are indicated by +++, --- $p < 0.001$; ++, -- $p < 0.01$; +, - $p < 0.05$; (+), (-) $p < 0.1$; N.S. (not significant) $p \geq 0.1$, with plus (minus) signs indicating the percentage is higher (lower) in the group in question than in the never smoker group. In addition, an estimate of the amount of bias due to the potential confounding effect of each risk factor was computed, as described in section 3. Due to the size

of the study, and lack of available time, it has not yet been possible to analyse fully all of the data, but results from a preliminary analysis of 17 variables, covering most of the aspects of health and lifestyle investigated by the survey, are presented below. The variables were chosen as being those which showed the most significant differences between all of the four smoking groups.

2. Differences Between the Four Smoking Groups

The preliminary results are presented in Table 1, which gives the total number at risk, the age-adjusted percentages of respondents in each category, and the direction and significance of any differences between the four exposure groups. Table 1 also shows estimates of the amount of bias which might arise due to smoking behaviour. It should be noted that a given difference in distribution is more likely to be detected as significant in women, not only because there were more women (5098) in total than men (3095), but also, and more so, because there were more women (1665) than men (634) in the base group of never smokers.

Social class

For both sexes, passive, ex and current smokers were of lower social class than never smokers ($p < 0.001$ for all three smoking groups). Passive smokers were particularly unlikely to be social class I, less so than smokers.

Alcohol consumption in previous week

The respondents were classified into categories of drinker according to the number of units of alcohol they had consumed in the previous week. The classification followed that used in national surveys (Dight, 1976; Wilson, 1980), so that for men the groupings were light 1-10 units; moderate 11-50 units; heavy 51+ units, and for women, light 1-5 units; moderate 6-35 units; heavy 36+ units. In both sexes, ex and current smokers were classified as heavier drinkers than never smokers ($p < 0.001$ for both groups). Passive smokers were also more likely to be heavier drinkers, although less so than past or current smokers ($p < 0.01$ for both sexes). Overall, women drank far less than men, with the median number of units of alcohol consumed the previous week being 3, 3, 4 and 5 for never, passive, ex and current smokers, compared to 8, 15, 10 and 14 respectively for the men.

Number of times fried food was eaten per week

In both sexes current smokers ate fried foods more often than never smokers ($p < 0.001$), while past smokers ate about the same. Passive smokers ate fried food more often than never smokers, and this association was stronger in women ($p < 0.001$) than in men ($p < 0.05$).

Number of times chips were eaten per week

The results for this food item were very similar to those for fried food in general, with consumption by both male and female ex-smokers being comparable to that of never smokers, and both passive and current smokers consuming chips more frequently per week than never smokers ($p < 0.001$ for passive and current smokers of both sexes).

Number of times sausages, meat pies and similar meat products were eaten per week

The consumption pattern for processed meat products was similar to that of chips and other fried food. In both sexes, passive smokers and current smokers had a higher frequency of consumption of these products per week ($p < 0.05$ and $p < 0.001$ respectively), while the consumption by past smokers was no different from that by never smokers.

Number of times salads were eaten per week in summer

In contrast with the food items previously discussed, male passive and current smokers showed a lower frequency of consumption of salads per week in summer ($p < 0.05$ and $p < 0.001$ respectively), but past smokers ate salads as often as never smokers. Among the women in the study, only the current smokers showed a different pattern of consumption, being less likely to eat salads frequently in summer than never smokers ($p < 0.001$), who ate them with a similar frequency to that of past and passive smokers. The overall pattern of consumption of salads in winter was similar to consumption in summer, although the frequency of consumption was reduced, with the majority of respondents only eating salads less than once, or once or twice a week, in winter, compared to once or twice a week, or most days, in summer (not shown in table).

Number of times breakfast cereal was eaten per week

Male passive, past and current smokers all ate breakfast cereal less frequently per week than never smokers ($p < 0.01$, $p < 0.05$ and $p < 0.001$ respectively). Women passive and current smokers also ate breakfast cereal less often than never smokers ($p < 0.05$ and $p < 0.001$ respectively), but past smokers showed no difference in their consumption of this food.

Number of cups of tea drunk per day

A higher number of cups of tea per day were drunk by men who were passive or current smokers than men who were never smokers ($p < 0.001$ for both groups), and there was also a tendency for past smokers to have a higher consumption of tea ($p < 0.1$). Only women who were current smokers showed a higher consumption of tea ($p < 0.001$), with the number of cups of tea drunk per day by passive and past smokers being comparable to that of never smokers.

Amount of sugar used in tea

As well as drinking more cups of tea than never smokers, male passive and current smokers were also more likely to put sugar in these drinks ($p < 0.01$ and $p < 0.001$ respectively). The same was true for women passive and current smokers ($p < 0.05$ and $p < 0.001$ respectively), but unlike ex-smoking men, who showed no difference from never smokers in their use of sugar in tea, women who were past smokers actually used less sugar than never smokers ($p < 0.05$).

Number of times jam and other preserves were eaten per week

Passive, past and current smokers of both sexes had a lower frequency of consumption of jams and similar preserves than that of never smokers ($p < 0.001$, $p < 0.05$ and $p < 0.001$ for male passive, past and current smokers respectively; $p < 0.01$, $p < 0.01$ and $p < 0.001$ for female passive, past and current smokers respectively). Current smokers of both sexes also appeared to eat other sweet foods, such as cakes, biscuits, sweets, puddings, yogurt and ice-cream, less frequently than never smokers (not shown in table).

Own health in general

Men who were passive, past or current smokers were all more likely to rate their health as being poorer for someone of their age than were never smokers ($p < 0.05$ for passive and past smokers, $p < 0.001$ for current smokers). Female past and current smokers were also more likely to rate their health as poorer ($p < 0.01$ and $p < 0.001$ respectively), but women who were passive smokers showed no difference from never smokers for this variable.

History of bronchitis

Compared with never smokers, current smokers were more likely ($p < 0.05$ males, $p < 0.001$ females) to have ever suffered from bronchitis but passive smokers were not. Ex-smokers were also more likely to have had bronchitis than never smokers but the difference was significant ($p < 0.05$) only for women.

History of depression/nervous illness

Male current smokers were more likely ($p < 0.001$) to have ever suffered from this illness than never, passive or ex-smokers, who showed no differences from each other. Among the women, current and past smokers were more likely to have a history of the disease ($p < 0.001$ for both groups), while the incidence in passive smokers was comparable to that of never smokers.

Suffered from cold/flu during previous month

Whereas the previous two questions referred to the respondents' entire medical history, this variable was designed to obtain information about illness in the recent past. Men who were current or passive smokers showed an increased incidence of colds/flu in the previous month ($p < 0.01$ for both groups), while ex-smokers did not show any significant differences from never smokers. This same pattern was seen in the women in the study, with current and passive smokers being more likely ($p < 0.01$ and $p < 0.05$ respectively) to have suffered from colds/flu recently than past and never smokers, who were similar to each other in this respect.

Lowest systolic blood pressure

Four measurements of systolic blood pressure were taken at one minute intervals from each other, and the lowest value for each respondent from any one of these four tests was used to create this variable. The median lowest systolic blood pressures were respectively 124, 125, 130 and 127 for the men, and 120, 120, 121, and 118 for the women. After adjustment for age, it was found that the lowest values for men and women who were passive smokers appeared to be higher than those for never smokers, and these differences were significant in both the men and the women ($p < 0.05$ for both sexes). The lowest systolic blood pressures of the past and current smokers were comparable to those of the never smokers. Similar overall results were obtained for lowest diastolic and mean arterial blood pressure (not shown in table). (N.B. The cut off point of 140 was used to indicate abnormal blood pressure, following WHO (1978). For females, the significant increase for passive smokers reflects a difference in the overall distribution, but the increase in the prevalence of values above 140 is only small and not significant).

Do you get enough exercise?

While men who were passive smokers were more likely than never smokers to think that they got enough exercise ($p < 0.01$), men who had given up smoking were less likely to agree with this statement ($p < 0.05$). Currently smoking men produced similar responses as never smokers. Women who had given up smoking were also less likely to think that they got enough exercise ($p < 0.01$), while passive and current smokers showed no differences from never smokers in their self-assessment of the amount of exercise they got.

Participation in physical activities in the previous fortnight

Respondents were shown a list of 17 physical sports and activities and asked if they had taken part in any of them in the previous fortnight. Among the men, current and past smokers were less likely to have taken part in any of the activities ($p < 0.001$ and $p < 0.05$ respectively), while passive smokers were just as likely as the never smokers to have done so. Female current smokers also appeared to take less physical exercise than the other groups ($p < 0.01$), who showed no differences from each other in their likelihood of having participated in one or more of the activities on the list.

Table 1
'HEALTH AND LIFESTYLE SURVEY'

Stratified by Age

		Male				Female				
		never	passive	ex	current	never	passive	ex	current	RR
REGISTRAR GENERAL SOCIAL CLASS										
	N	612	209	825	2181	1624	651	936	1771	
SCI	%A	9.17	1.38	5.11	3.92	7.82	1.77	7.37	3.98	0.77
SCII	%A	31.22	17.02	26.53	19.76	28.79	23.05	23.26	17.87	0.94
SCIII NON-MAN	%A	14.27	14.09	13.93	11.04	17.08	18.11	14.97	14.00	1.21
SCIII MANUAL	%A	30.96	40.20	35.97	38.93	29.00	32.76	33.60	37.59	1.71
SCIV	%A	10.61	20.13	13.71	19.10	14.55	18.81	16.02	19.39	2.46
SCV	%A	3.78	7.18	4.75	7.25	2.77	5.50	4.78	7.17	2.87
Bias			1.20	1.08	1.18		1.11	1.06	1.15	
	P		+++	+++	+++		+++	+++	+++	
ALCOHOL CONSUMPTION IN PREVIOUS WEEK										
	N	633	219	832	2217	1665	668	954	1809	
NON-DRINKERS	%A	30.08	27.42	16.53	18.06	46.43	40.49	34.11	35.18	1.24
LIGHT	%A	41.93	37.30	41.48	36.17	38.49	39.42	41.33	36.15	2.00
MODERATE	%A	26.88	28.76	38.13	38.51	14.95	20.09	24.56	27.95	3.17
HEAVY	%A	1.12	6.52	3.86	7.25	0.13	0.00	0.00	0.71	3.93
Bias			1.07	1.14	1.16		1.06	1.11	1.14	
	P		++	+++	+++		++	+++	+++	
FRIED FOOD EATEN PER WEEK										
	N	632	220	832	2218	1665	668	954	1808	
at least MOST DAYS	%A	18.85	23.44	21.51	29.53	8.02	11.93	8.26	13.60	2.00
Bias			1.04	1.02	1.09		1.04	1.00	1.05	
	P		+	N.S.	+++		+++	N.S.	+++	
CHIPS PER WEEK										
	N	632	220	831	2216	1665	667	954	1809	
at least MOST DAYS	%A	16.62	27.92	17.31	24.48	6.74	9.20	8.03	13.74	2.00
Bias			1.10	1.01	1.07		1.02	1.01	1.07	
	P		+++	N.S.	+++		+++	N.S.	+++	
SAUSAGES,MEAT PIES ETC PER WEEK										
at least 1 OR 2	N	632	220	832	2216	1663	667	954	1809	
PER WEEK	%A	62.74	73.48	63.49	68.64	47.60	54.00	48.58	54.72	2.00
Bias			1.07	1.00	1.04		1.04	1.01	1.05	
	P		+	N.S.	+++		+	N.S.	+++	
SALADS PER WEEK IN SUMMER										
	N	632	220	831	2218	1665	667	954	1809	
at least MOST DAYS	%A	57.73	46.28	58.67	49.36	69.86	66.90	71.49	65.30	2.00
Bias			0.93	1.01	0.95		0.98	1.01	0.97	
Bias 2			1.08	0.99	1.06		1.02	0.99	1.04	
	P		-	N.S.	---		N.S.	N.S.	---	
BREAKFAST CEREAL PER WEEK										
	N	632	220	831	2216	1664	667	954	1809	
at least ONCE A DAY	%A	38.71	34.27	37.27	26.29	36.36	30.25	36.00	21.81	2.00
Bias			0.97	0.99	0.91		0.96	1.00	0.89	
Bias 2			1.08	1.03	1.12		1.04	0.98	1.12	
	P		--	-	---		-	N.S.	---	
CUPS OF TEA DRUNK PER DAY										
	N	634	220	831	2216	1663	668	954	1805	
at least FIVE	%A	37.33	48.76	40.40	50.76	36.72	39.28	38.87	45.78	2.00
Bias			1.08	1.02	1.10		1.02	1.02	1.07	
	P		+++	(+)	+++		N.S.	N.S.	+++	

Table 1 (cont.)
'HEALTH AND LIFESTYLE SURVEY'

Stratified by Age

		Male				Female				
		never	passive	ex	current	never	passive	ex	current	RR
AMOUNT OF SUGAR IN TEA (TEASPOONS)										
	N	526	192	764	1966	1479	575	859	1538	
more than ONE	%A	25.79	38.52	28.79	44.28	11.55	15.39	10.59	24.58	2.00
Bias			1.10	1.02	1.15		1.03	0.99	1.12	
	P		++	N.S.	+++		+	-	+++	
JAM ETC PER WEEK										
	N	632	220	832	2215	1663	667	954	1809	
at least MOST DAYS	%A	38.16	21.50	34.28	29.19	39.81	35.09	34.59	29.31	2.00
Bias			0.88	0.97	0.94		0.97	0.96	0.92	
	P		---	-	---		--	--	---	
OWN HEALTH IN GENERAL										
	N	631	220	829	2213	1657	668	950	1800	
FAIR or POOR	%A	17.70	27.50	24.91	32.24	23.88	24.37	27.68	33.88	2.00
Bias			1.08	1.06	1.12		1.00	1.03	1.08	
	P		+	+	+++		N.S.	++	+++	
HAD BRONCHITIS										
	N	634	220	832	2218	1665	668	954	1809	
YES	%A	8.74	7.98	11.30	11.61	8.33	8.46	11.86	14.19	2.00
Bias			0.99	1.02	1.03		1.00	1.03	1.05	
	P		N.S.	N.S.	+		N.S.	++	+++	
HAD DEPRESSION/NERVOUS ILLNESS										
	N	634	220	832	2218	1665	668	954	1809	
YES	%A	8.66	10.60	11.46	13.58	16.65	16.83	24.17	28.33	2.00
Bias			1.02	1.03	1.05		1.00	1.06	1.10	
	P		N.S.	N.S.	+++		N.S.	+++	+++	
COLDS/FLU LAST MONTH?										
	N	634	220	832	2218	1665	668	954	1809	
YES	%A	26.48	31.62	29.82	33.64	29.37	35.03	32.80	34.28	2.00
Bias			1.04	1.03	1.06		1.04	1.03	1.04	
	P		++	N.S.	++		+	N.S.	++	
LOWEST SYSTOLIC BLOOD PRESSURE										
	N	532	175	719	1875	1314	552	764	1452	
> 140	%A	21.15	25.88	21.14	21.43	15.91	16.42	15.30	16.42	2.00
Bias			1.04	1.00	1.00		1.00	0.99	1.00	
	P		+	N.S.	N.S.		+	N.S.	N.S.	
GET ENOUGH EXERCISE										
	N	624	217	827	2194	1638	659	942	1789	
YES	%A	56.21	66.75	48.94	54.05	51.85	53.82	48.24	53.83	2.00
Bias			1.07	0.95	0.99		1.01	0.98	1.01	
Bias 2			0.93	1.05	1.01		0.99	1.03	0.99	
	P		++	-	N.S.		N.S.	--	N.S.	
ACTIVITIES IN LAST FORTNIGHT										
	N	633	220	832	2216	1663	668	954	1809	
YES	%A	46.74	39.73	42.03	37.82	38.68	38.83	36.03	34.64	2.00
Bias			0.95	0.97	0.94		1.00	0.98	0.97	
Bias 2			1.05	1.03	1.06		1.00	1.02	1.03	
	P		N.S.	-	---		N.S.	N.S.	--	

3. Effects of bias from confounding factors

Suppose we are comparing risk of some disease in two smoking groups, say passive and never smokers, and suppose that we know the age-adjusted frequencies of exposure of a three level risk factor and that the relative risks of the disease associated with the risk factor compared to some base level are as follows:

Exposure to risk factor	Never smokers	Passive smokers	Relative risk
Low	50%	20%	1 (base)
Middle	30%	40%	2
High	20%	40%	3

Compared with a population consisting of 100% subjects with low exposure, one can readily calculate that the passive smokers would have a relative risk of (0.20 x 1 + 0.40 x 2 + 0.40 x 3) = 2.2, while the never smokers would have a relative risk of (0.50 x 1 + 0.30 x 2 + 0.20 x 3) = 1.7, i.e. in the absence of any true effect of passive smoking, the passive smokers would be expected to have a risk of disease which is higher by a factor 2.2/1.7 = 1.29 than that of the never smokers simply due to confounding by the risk factor.

Formally, the bias due to confounding is given by

$$\text{Bias} = \sum_{j=1}^{n}(P_{2j}\ R_j) / \sum_{j=1}^{n}(P_{1j}\ R_j)$$

where there are n levels of the factor (j=1,2...n), R_j is the relative risk associated with each level, and P_{2j} and P_{1j} are the frequencies of each level in the two groups being compared.

Estimates of the frequencies are available from Table 1, but the survey provides no data on risk of disease. Rather than try to obtain, for various diseases, independent estimates of relative risk by level of each risk factor studied we prefer to try to quantify potential for bias by attempting to answer the question "Suppose exposure to the risk factor doubled risk of a disease, how much bias due to confounding would arise when comparing the smoking groups?" For a two level risk factor - non-exposed (relative risk 1) and exposed (relative risk 2) - the

calculation of bias is straightforward. For two risk factors with multiple levels, alcohol and social class, however, the calculation was amended. In this case the procedure used was as follows:

i) choose the level of exposure which most nearly divides the population into two equal halves, i.e. a cut-point so that the frequency of subjects above the cut-point is as close to 50% as it can be.

ii) assign an average relative risk of 2 to subjects above the cut-point and 1 to other subjects.

iii) interpolate linearly, in a plot of log risk against cumulative frequency of exposure, to assign relative risks to each level of exposure.

The estimated values of these potential biasses are shown in Table 1 together with the assumed values of the relative risks, shown in the column headed RR. It should be noted that though for most of the variables, increasing exposure is normally in the direction of increasing risk to lung cancer, cardiovascular disease, or adverse health in general, for some of the variables (salads, breakfast cereal, get enough exercise, and activities in last fortnight) the association is likely to be in the reverse direction. Here, on an additional line, marked Bias 2, the bias assuming that exposure halves rather than doubles risk is shown.

Under these assumptions it can be seen that the bias when comparing never and passive smokers is often in the range 1.04-1.10, being largest for social class in males, when it is as high as 1.20. To illustrate further the magnitude of the potential bias Table 2 shows for each sex separately the biasses in rank order (Bias 2 being shown for the four variables where this is calculated), with those for factors not not statistically significant at the 95% confidence level shown in brackets. The actual magnitude of bias for any factor will, of course, vary depending on the strength of the relationship (if any) to the disease being studied. However, the fact that two-fold or greater differences in risk of various diseases have been reported in relation to exposure to many of the risk factors studied, and the fact that biasses due to confounding from multiple risk factors will be larger than from single risk factors, underlines the crucial importance of careful adjustment for

Table 2

Potential biasses* associated with various risk factors

Males		Females	
Factor	Bias	Factor	Bias
Social class	1.20	Social class	1.11
Sugar in tea	1.10	Alcohol consumption	1.06
Chips**	1.10	Breakfast cereal	1.04
Breakfast cereal	1.08	Colds/flu	1.04
Cups of tea	1.08	Fried food	1.04
Own health	1.08	Sausages etc	1.04
Salads in summer	1.08	Sugar in tea	1.03
Alcohol consumption	1.07	Chips**	1.02
Sausages etc	1.07	(Cups of tea	1.02)
(Activities	1.05)+	(Salads in summer	1.02)
Colds/flu	1.04	(Activities	1.00)
Fried food	1.04	(Bronchitis	1.00)
Systolic blood pressure	1.04	(Depression	1.00)
(Depression	1.02)	Systolic blood pressure	1.00++
(Bronchitis	0.99)	(Own health	1.00)
Exercise	0.93	(Exercise	0.99)
Jam etc	0.88	Jam etc	0.97

* See text for details of method by which this was calculated

** For US readers, this is equivalent to french fries, not what we call potato crisps

+ Brackets indicate non significant associations

++ See note in text of section 2 concerning blood pressure

potential confounding variables when assessing the relationship of passive smoking to diseases such as lung cancer, where reported relative risks tend to average about 1.2.

Table 2 also shows that differences between passive and never smokers are virtually always in the direction of passive smokers being expected to have a higher risk due to exposure to other risk factors. Thus, inter alia, passive smokers were of lower social class, drank more alcohol, ate more fatty foods, ate less salads (and probably also vitamins A and C, though this has still to be investigated), and had higher blood pressure. The only significant differences in the reverse direction were that passive smokers ate less jam and other preserves and reported they were more likely to get "enough" exercise (although the findings for activities in the last fortnight - see Table 1 - suggested that they did not actually take more exercise, perhaps having a lower requirement for "enough").

The estimates of bias can be viewed as indices of the extent and direction of the association between the variables and the smoking category. It is notable that, for virtually all the significant associations, the relationship between the variable and passive smoking is in the same direction as that between it and current smoking, and that the strength of the relationship for passive smoking is a substantial part (sometimes greater) of that with current smoking. Though there are some minor exceptions, the results suggest strongly that wherever a significant difference between current and never smokers is reported for some risk factor, one is likely to find a difference in the same direction, though probably somewhat smaller, between passive and never smokers.

4. General Conclusions

Current smokers differ significantly from never smokers in exposure to a variety of independent risk factors.

The difference is virtually always in the direction of predicting an increased risk of disease in smokers independent of their smoking.

Where such a difference is seen, a difference in the same direction is nearly always seen in relationship to passive smoke exposure.

For many risk factors, the magnitude of the difference in exposure in relation to passive smoking is sufficient to cause bias large enough to be important, when compared with the magnitude of the relative risk associated with passive smoking for diseases such as lung cancer.