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Environmental Tobacco Smoke

A commentary on some of the evidence provided by OSHA in support of their proposed rules

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1. Introduction

I am an Independent Consultant in Statistics and Epidemiology, providing advice to a wide range of clients, including the tobacco industry. I have published some 150 papers and letters, listed in my CV attached as Annex A. Possible health effects of environmental tobacco smoke (ETS) have been a major interest of mine for some 15 years, and in 1992 I published a book, "Environmental Tobacco Smoke and Mortality" (CV ref 114), which, after a most detailed review of the evidence then available, concluded that "there is no convincing epidemiological evidence that exposure to ETS results in an increased risk of death from cancer, heart disease or any other disease in non-smokers." Having studied the additional evidence published since that time my conclusions remain unchanged. I believe the Environmental Protection Agency (EPA) was wrong to classify ETS as a human carcinogen and consider the EPA's estimate of 3,000 lung cancer deaths a year in the US arising from ETS to be totally unscientific. I expressed this view in submissions to the EPA on both drafts of the EPA report. A paper shortly to be presented at the 1994 American Statistical Association Conference summarizing my current views on lung cancer and making clear why the EPA report is unsound is attached as Annex B.

I was provided by the Tobacco Institute with a copy of OSHA's proposed rules on Indoor Air Quality, appearing at pp.15968-16039 of the Federal Register, Vol 59, No 65, and asked for my comments. I have concentrated on the sections relating to environmental tobacco smoke and have mainly restricted my attention to sections relating to the epidemiological evidence.

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My detailed comments are presented in six further annexes:

Annex C The claim that ETS exposure at work is greater than ETS exposure at home

Annex D Pulmonary effects in adults

Annex E Cardiovascular effects

Annex F Reproductive effects

Annex G Cancer

Annex H The relevance of dietary nicotine to the evaluation of cotinine as a biomarker for ETS.

Before summarizing my detailed comments, in sections 3 to 8 below, I first give some general comments on the evidence provided by OSHA.

2. Some general comments

Although I had a number of criticisms of the EPA report, they are nothing to the criticisms I have of the OSHA report, which any self-respecting scientist would be absolutely ashamed to produce. There are a number of major and persistent problems, including:

(i) Falsely claiming that studies indicate an association of ETS with an adverse health effect when in fact they do not do so. In some cases references cited in support of OSHA's position do not even relate to the issue under discussion. While this may result from simple errors in cross-referring, there are a number of cases where a relevant study is considered and where the statements made by OSHA are unjustified.

(ii) Failure to cite many studies providing relevant evidence. A large number of these uncited studies report results which do not fit in with the views put forward by OSHA. In some cases whole areas of evidence that do not fit in are ignored totally.

(iii) Failure to point out obvious weaknesses in many of the studies reporting an association of ETS with an adverse health effect.

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OSHA pays so little attention to study quality as to give the impression that any study reporting an association can be assumed to be valid.

(iv) Failure to understand the extent to which biasing factors can affect the interpretation of epidemiological studies. In some sections possibilities of bias are not considered at all. In others they are given only the most cursory attention, with some major potential sources completely unconsidered or under-estimated.

(v) Failure to explain the arguments leading to the conclusions reached, or to give adequate details of the methodology used in the review process.

Examples of all these points are given in the sections that follow and in Annexes C-G. The overall impression is of an extremely poor piece of work put together sloppily by authors who had very strong preconceptions that ETS was harmful, and did not actually want to carry out a systematic and unbiased review. There are weaknesses certainly in previous reviews conducted in the US, by the Surgeon General, the National Academy of Sciences, and by EPA, but they are excellent documents compared to this - which stands on its own as being quite appallingly unscientific and biased.

3. <u>The claim that ETS exposure at work is greater than ETS exposure at home</u>

In a number of places OSHA claims that exposure to ETS is greater at work than at home. In some places OSHA claims it is substantially greater. This claim is then used to support the argument that risks associated with workplace exposure must be greater than those associated with at home exposure, which has been more extensively studied.

As <u>Annex C</u> makes clear, this claim is totally unjustified. Exposure is the product of duration and concentration. To quantify it, two methods are appropriate, personal monitors and/or

biomarkers (in particular cotinine, which derives largely from exposure to tobacco). Annex C gives evidence from nine studies using cotinine and two using personal monitors. With one exception, an old Japanese study with various technical weaknesses, all the studies showed that the home was a greater source of exposure than the workplace. One of these was a study conducted by IARC in 13 centres located in 10 countries.

It is quite remarkable that OSHA does not cite any of this evidence at all. Instead OSHA bases its conclusions mainly on evidence from studies that did not measure exposure at all. OSHA places great weight on the CAP study, which recorded only time of exposure to ETS, with no data actually recorded on concentration. Tables presented by the authors of this study did not actually suggest that length of exposure at work was any greater anyway, but OSHA presented tables of its own purportedly indicating the contrary. These tables (III-8 and 9) are clearly totally wrong, since they suggest (contrary to the obvious facts) that everyone is exposed to ETS in one and only one of four locations (home, work, other indoor or outdoor), noone being totally unexposed and noone being exposed in two or more locations!!

4. Pulmonary "effects" in adults

Previous reviewers, including a very recent review by members of IARC, have not considered that the evidence that ETS exposure affects pulmonary function, chronic respiratory symptom incidence or risk of development of COPD is conclusive. In contrast, OSHA concludes such effects have been demonstrated. Although one would have thought that such a major change of opinion would require justification by a careful review of the evidence, OSHA in fact presents only a cursory and inadequate look at some of the evidence. As Annex D makes clear, much relevant evidence, most of which runs counter to OSHA's conclusions, is not cited. Some of the studies OSHA does cite as showing an association with ETS exposure in fact do not do so, and others are cited as showing an association without mentioning that this was only for a subset of the data and/or for a small number of symptoms out of a large number studied.

In line with the rest of the report, OSHA does not refer to any weaknesses of specified studies and gives only the most cursory attention to sources of bias common to many or all of the studies.

5. Cardiovascular "effects"

Though there are exceptions, most published reviews, and all those prepared by national authorities, have concluded that there is insufficient evidence to support a causal relationship between ETS and heart disease. OSHA concludes that an effect has been demonstrated, and goes so far as to estimate numbers of deaths per year occurring as a result of workplace ETS exposure. Just as for pulmonary "effects," one might have thought that OSHA would have carefully justified its position. OSHA's Federal Register notice does not do so, and the attention given to the epidemiological data is very cursory indeed. As Annex E makes clear, OSHA appears to be ready to equate any statistically significant association as evidence of cause and effect. No attention is given to major weaknesses specific to a number of the studies, including the Helsing study used in the OSHA risk assessment. Nor is any mention made at all of major potential sources of bias, such as confounding by other risk factors, misclassification of smoking habits bias, and publication bias, when interpreting the overall evidence.

The preliminary quantitative risk assessment, when it considers heart disease, is totally inadequate. Some of the studies cited as separate are in fact actually the same study, while some other published studies are not cited at all. No explanation is given as to how studies are described as "positive", "equivocal positive" and "equivocal", and indeed examination of the evidence from the individual studies actually suggests none can be classified as positive using any sort of sensible criteria. A combined relative risk estimate of 1.24 to 3.00 is plucked out of the air, and bears little or no relationship at all to the magnitude of the observed association based on all the available data which, even ignoring any sources of bias or study weakness, gives an overall estimate of 1.28 with an upper 95% confidence limit of 1.39. To suggest ETS exposure might triple risk of heart disease is ludicrous. Even a 24 percent

increase is rather implausible, bearing in mind that active smoking, which involves vastly higher exposure to smoke constituents than does ETS, involves only an 80 or 90 percent increase (American Cancer Society Cancer Prevention Study II data). Note that these estimates are based on exposure at home, mainly from the spouse. OSHA conceals the important fact that six studies actually provide direct evidence on risk of heart disease specifically in relation to workplace ETS exposure, none of them showing a statistically significantly higher risk of heart disease in lifelong nonsmokers working with a smoker compared to those not working with a smoker.

The actual calculation of risk for nonsmoking workers exposed to ETS at the workplace suffers from a number of glaring errors. It inappropriately uses ancient data from the Framingham study to estimate overall heart disease rates in nonsmokers, ignoring the massive decline in risk that has occurred in the last 30 years. It relies on risk estimates relating to at home ETS exposure, rather than relating to workplace ETS exposure. It relies on risk estimates from a study by Helsing that has a number of major weaknesses. It is certainly not true that, as OSHA states, the Helsing study is a "large, population-based" study "whose results can be generalized to the general public" or that "by design" it "controlled for misclassification to a large degree." The risks presented by OSHA in Table IV-10 are not actually, as stated, referable to ETS exposed nonsmoking workers, but are referable to all nonsmoking workers. Nor are they risks; they are excess risks. Finally, the calculations of lifetime risk falsely assume that at age 20-34 one has the same risk as at age 35-64.

6. Reproductive effects

In Annex F I consider in detail the various reproductive effects that OSHA claims or implies are associated with exposure of the mother to ETS during pregnancy. These include low and reduced birthweight, increased perinatal mortality, increased risk of miscarriage and congenital abnormalities, increased risk of cancer in childhood and adulthood, and increased risk of various other long-term sequelae in childhood and adulthood.

Overall, the evidence presented is blatantly biased, reference never being made to any studies that did not report a positive association. Additionally, a causal effect is frequently inferred from the results of only one study, there being no discussion whatsoever of any alternative hypotheses that might explain the reported association. On several occasions the references used do not really support the statements made by OSHA, and in some cases they actually appear to contradict them. There is also a tendency to mislead by reference to associations of active smoking with endpoints (such as increased perinatal mortality), trying to suggest indirectly such an association exists with ETS exposure, when in fact there is no evidence that this is so.

As a result of this, OSHA gives the reader a totally false impression of the pertinent data. For one of the most investigated endpoints, low birthweight, five studies only are cited, all of which had weaknesses and two of which were clearly not statistically significant. OSHA conceals the fact that there are at least 14 published studies reporting no significant association between ETS and birthweight, and one that reports a significantly increased birthweight in the ETS exposed group. Bearing in mind inter alia the difficulties of taking potential confounding variables into account, it is clear that the overall evidence in no way demonstrates a cause-and-effect relationship, but OSHA leaves the impression that it does.

Annex F includes a detailed discussion of three other endpoints where OSHA selectively cites data and gives a total misrepresentation of the evidence. For birth defects (Appendix Attachment 1 to Annex F), childhood cancer (Appendix Attachment 2) and adult cancer, it is quite clear that the total evidence, when properly considered, shows little or no indication of an association, let alone a cause-and-effect relationship. For lung cancer, OSHA cites three references in support of the view that ETS exposure in utero or in childhood may increase an individual's cancer risk in nonsmokers. Of the three references, two actually

reported no association at all, while the one that did only reported it in a subset of the data. There are actually 15 studies in which risk of lung cancer of never smokers in relation to childhood ETS exposure has been investigated. The overall data show no indication whatsoever of an association, with a meta-analysis providing a combined relative risk estimate slightly less than one. To attempt to suggest that an association exists when the overall evidence is flat as a pancake is a denigration of science.

7. Cancer

Although section II.C.6 is entitled "Cancer", the epidemiological evidence discussed is concerned only with lung cancer. As the evidence relating ETS to cancer at sites other than the lung is fragmentary and inconclusive, and as OSHA does not discuss it, I will not concern myself with it in these comments, but restrict my attention to lung cancer.

Annex G is mainly concerned with the direct epidemiological evidence in relation to ETS exposure. However, before discussing it in detail, I first make it clear that neither the experimental evidence in animals nor the dosimetric argument based on the "chemical similarity between mainstream smoke and ETS" coupled with "the unequivocal causal association between active tobacco smoking and lung cancer in humans" provides proof that ETS causes lung cancer. The animal evidence does not include any appropriately conducted long-term inhalation study demonstrating clearly that ETS causes lung cancer. The dosimetric argument may suggest the possibility that ETS might cause lung cancer, but it certainly does not prove that it does so or that, as OSHA claims, it is plausible it does so.

There are a large number of weaknesses in how OSHA has evaluated the evidence on lung cancer. In the first place, the list of studies considered is somewhat inappropriate. Of the 31 studies included in Table IV-1, two should be removed as they provide essentially no useful data, one should be removed as it has been superseded by another more recent paper (also included) on the same

study, and one should be updated by a more recent paper describing full rather than partial results. Nine further studies, omitted by OSHA, should be included.

Second, OSHA claims to have carried out a critical review of the evidence but gives no details at all of the methodology that was used. Studies are classified as "positive", "equivocal positive trend" or "equivocal" using unstated criteria. Some studies included as positive, presumably because OSHA believes they show a statistically significant relationship, do not do so. One study, the largest ever conducted at the time it was published, was cited by OSHA as "positive" despite the fact that relative risk estimates relating to all major indices of exposure showed no evidence whatsoever of an increase. In fact, the relative risk estimate for marriage to a smoker, the index apparently favoured by OSHA, was 1.0! It is notable that EPA was criticized for failing to cite results from this null study, although EPA staff must have known about it when preparing the EPA report. OSHA avoids the problem by a different method; claiming it is "positive" when it is not.

Third, OSHA claims falsely that the relative risk of lung cancer in relation to marriage to a smoker is in the range 1.20 to 1.50, giving no details as to how this figure was computed. According to my calculations the overall evidence for marriage to a smoker from the 37 published studies gives a meta-analysis estimate of only 1.14 (95% confidence interval 1.04-1.23). And this is before any downward adjustment for bias due to the effects of such factors as smoking habit misclassification and uncontrolled confounding by other risk factors.

Fourth, OSHA restricts attention, without any justification whatsoever, to results relating to husband's smoking as the index of ETS exposure. OSHA is directly concerned with the health of workers and claims that the workplace is a more important source of ETS exposure than is the home. Since considerable attention has been given to the possibility that use of husband's smoking as an index may produce biased results arising from the tendency of husband and

wife to be concordant in respect of smoking and other lifestyle factors, it is quite amazing that OSHA never considers the direct evidence relating ETS exposure in the workplace to risk of lung cancer in nonsmokers. I am aware of 13 studies that have investigated this relationship. Two of these studies reported finding no association but gave no detailed results. Combining relative risk estimates from the other studies by meta-analysis gives a combined estimate of 1.02 (95% confidence limits 0.93-1.12), which shows no real relationship at all. To ignore completely direct evidence showing no association between ETS exposure at the workplace and lung cancer risk and to rely solely on indirect, probably biased, evidence seems totally unjustified. It must be regarded as a blatant attempt to conceal the true evidence from the reader.

Fifth, OSHA totally ignores the question of dose-response, when one would have thought that evidence on this is quite crucial to the issue. As discussed in Annex G, although the association between heavy spousal smoking and lung cancer is in fact somewhat stronger than that between average spousal smoking and lung cancer, care needs to be taken in interpreting this observation. There are a number of sources of bias that will produce an artificial dose-response relationship.

Sixth, OSHA obscures evidence on the relationship of ETS to the various histological types of lung cancer. It is not made clear that the association with active smoking is much stronger for squamous/small-cell lung cancer than it is for adenocarcinoma/large-cell lung cancer, suggesting that if an association with ETS is evident, it would be much more likely to be evident for squamous/small-cell lung cancer. Nor does OSHA make clear that in fact the data conflict with this expectation. Though some studies do report data more consistent with a relationship only with squamous/small-cell lung cancer, as many other studies report the opposite, an apparent relationship only with adenocarcinoma/large-cell lung cancer.

Finally, and most importantly, OSHA grossly under-estimates the various possibilities of bias in the epidemiological studies. OSHA's whole discussion of bias is far too short given the enormous attention given to it in the literature. Furthermore a number of statements made in this discussion are misleading or totally erroneous. For instance, it is stated that "biases that may be problematic in case-control studies are not a problem in prospective studies," a conclusion that does not apply generally to all types of bias, but applies only to one specific sort of bias (that resulting from incorrect recall of exposure). Furthermore it is also wrongly, and very misleadingly, stated that biases common to all, or most, of the studies are not likely to exist except for one specific form of bias (that resulting from the comparison group having non-zero ETS exposure) that results in under-estimation of the true relative risk. Of course it is possible that some common biases may lead to over-estimation of the true relative risk (vide infra). OSHA also gives no justification for the view that the three sources of bias discussed in the Federal Register notice (publication bias, misclassification bias, recall bias) are of minor importance, and fails to refer at all to some important sources of bias.

In Annex G I carefully consider five types of bias. The first three are:

(i) Publication bias. There are two pieces of evidence that suggest such a bias exists. One is the fact that the studies with the smallest number of deaths virtually all tend to produce unusually high relative risk estimates, consistent with failure to publish findings from small studies that produce low relative risk estimates. Secondly, one knows the American Cancer Society has a huge database (CPS-II) with relevant data, but has not yet published results.

(ii) Recall bias. Since all studies have relied on questionnaire data for ETS exposure, recall bias must be a possibility. Arguing, as OSHA does, that the similarity of results from

case-control and prospective studies rules out recall bias is invalid, as there is so little useful data from prospective studies.

(iii) Study weaknesses. OSHA never even suggests that any of the epidemiological studies discussed and relied upon in the Federal Register notice might have fundamental weaknesses that render interpretation difficult or impossible. In fact about half of the studies can be classified as having a serious weakness. I point out in Annex G that these 16 studies contain all 12 of the studies with the highest relative risk estimates for husband's smoking. A meta-analysis of results from the studies without serious weaknesses does not give a significantly increased relative risk estimate.

The last two types of bias are given more detailed attention in Annex G as I consider both of particular importance. These are:

(iv) Misclassification of active smoking status. I have presented arguments elsewhere putting forward the viewpoint that the tendency of some subjects to fail to report current or past smoking, coupled with the tendency of smokers to marry smokers, will cause material bias to relative risk estimates in studies where spousal smoking is used as the index of ETS exposure. In Appendix Attachment B of Annex G I extend these arguments further, underlining the importance of such misclassification bias. I counter the arguments of A J Wells given in the EPA report that such bias is only minor, and introduce new evidence showing that misclassification rates are very high in Japan, and suggesting they may also be high in other Asian countries.

(v) Uncontrolled confounding by other risk factors. It is quite astounding that OSHA fails to mention this possibility at all, as it is a very important one indeed, worthy of very serious consideration. There are two main issues here. The first issue relates to the "failure to use relevant denominators."

A number of studies using marriage to a smoker as the index of ETS exposure have failed to restrict attention to married subjects, thus essentially confusing possible effects of marital status with effects of ETS exposure. Similarly, studies of workplace exposure have often failed to restrict attention to the working population, and more subtly studies of household ETS exposure have always failed to take account of household size in analysis. Both failures may result in bias.

The second issue, and a particularly important one, lies in the growing evidence that nonsmokers married to smokers differ from nonsmokers married to nonsmokers in many ways, and that such differences tend systematically to be in the direction of predicting an increased risk of many diseases, including lung cancer. Evidence for this is summarized in my 1992 book and in a paper soon to appear in the Journal of Clinical Epidemiology, attached as Appendix Attachment C to Annex G. Dietary factors, particularly high fat consumption and low fruit and vegetable consumption, are of particular importance as potential confounders, and it is interesting to note that recent studies in nonsmokers have shown that lung cancer is far more strongly related to these factors than it is to ETS. Calculations given in the Journal of Clinical Epidemiology paper suggest strongly that bias due to uncontrolled confounding by dietary and other risk factors is likely to be of considerable practical importance.

When one is talking of an overall unadjusted relative risk estimate for husband's smoking of 1.14, and one has two sources of bias, misclassification of smoking habits and uncontrolled confounding by dietary and other risk factors, both of which can easily generate spurious relative risks in excess of 1.10, it is self-evident that OSHA cannot defend a view that bias and confounding are of minor importance. This view is further undermined by consideration also of publication bias, recall bias and bias due to specific study weaknesses.

Finally, problems should be noted in regard to the quantitative risk assessment for lung cancer. A number of these (failure to describe review methods, failure to define "positive" studies, etc., expression of risk in Table IV-9 using the wrong denominator, and assuming risks for 20-34 year olds are similar to those for 35-64 year olds) have already been referred to in section 5 when considering cardiovascular disease. There are some other points specific to lung cancer, however. One is use of an estimate for the US lung cancer rate in nonsmokers that seems too high compared with published data. The others relate to use of the Fontham data for the estimation. This study, conducted predominantly in California, may well have produced results that, contrary to OSHA's view, cannot be generalized to the US population. Furthermore, though it is stated that the study "controlled for misclassification to a large degree", I discuss reasons, in Annex G, why this control may in fact have been inadequate. Finally, it is striking that OSHA uses Fontham's estimate for workplace exposure when, as noted above, the overall evidence on lung cancer and workplace exposure produced a meta-analysis relative risk close to unity. To choose data from one study that happened to produce an atypically high relative risk estimate cannot be justified.

Overall OSHA's treatment of lung cancer is very inadequate and misleading, and OSHA's risk estimation accordingly is valueless.

8. Dietary nicotine

OSHA sought "comment and data on whether dietary intake of nicotine should be considered a significant factor in modelling nicotine metabolism for assessing risk due to ETS exposure". In Annex H I review the evidence here and make it clear that though nicotine is present in various solenaceous vegetables, it is at a very low level compared to nicotine in tobacco. Plausible levels of dietary nicotine intake can at best produce cotinine levels consistent with relatively low ETS exposure.

9. Conclusion

I can understand OSHA's wish to protect workers against hazards at work. I can also understand that, in view of various claims made in the literature and in the media, various members of OSHA may be concerned about the possibility that ETS exposure at work may be harmful, and some may genuinely believe harm does occur. It is not surprising, therefore, that OSHA should consider the possibility of issuing regulations to protect workers against ETS exposure. As part of such consideration, however, any reputable regulatory authority should conduct a careful review of the evidence to justify its proposed actions. OSHA has not done so. Instead, OSHA has have thrown together a collection of "evidence" with the hope that it might be deemed to be adequate justification. This collection is poorly structured, with little or no explanation being given of the source of various statements made or of how conclusions were drawn from the material included. It is also full of errors. More seriously, it is quite appallingly biased, with evidence inconsistent with OSHA's views often being ignored completely, and little or no consideration being given to the possibility that positive associations of specific health endpoints with ETS exposure might be explicable in terms of the various sources of bias that commonly occur in epidemiological studies. The end does not justify the means, and OSHA should be ashamed of attempting to corrupt science for what some may see as a "good" cause.

In my view, OSHA should immediately withdraw its proposal, and should then carry out a proper, balanced scientific review of the evidence. Only if that review provides an adequate case should OSHA consider reinstating the current proposal. If OSHA does not go down this path, any scientific reputability OSHA may have had will disappear forever.

10. Acknowledgements

I thank my colleagues Mrs. B A Forey and Miss A Thornton, who provided invaluable assistance in assembling these comments. However I alone bear full responsibility for them. I also thank Mrs. P Wassell for typing this manuscript.

Please note the following:

Annex A	Curriculum Vitae	Can be accessed via the staff page of our Web Site
Annex B	Lung cancer and ETS: Is the epidemiologic evidence conclusive	Available on request
Annex C	The claim that ETS exposure at work is greater than ETS exposure at home	Available on request
Annex D	Pulmonary effects in adults	Available on request
Annex E	Cardiovascular effects	Available on request
Annex F	Reproductive effects	Available on request
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