IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS VOLUME 83 (2004)

A COMMENTARY ON THE SECTION OF THE MONOGRAPH RELATED TO INVOLUNTARY SMOKING

Author : P N Lee

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P N Lee Statistics and Computing Ltd,
17 Cedar Road, Sutton, Surrey SM2 5DA
Tel: +44 (0) 2086428265
Fax: +44 (0) 2086422135
E-mail: PeterLee@pnlee.demon.co.uk

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EXECUTIVE SUMMARY

IARC considers that involuntary smoking (ie. ETS) is Carcinogenic to Humans, a Group 1 carcinogen. This conclusion crucially depends on IARC's evaluation that there is sufficient evidence that ETS causes lung cancer in humans, since IARC clearly considers the evidence that ETS causes other cancer in humans to be inconclusive. IARC also considers that there is sufficient evidence of the carcinogenicity of sidestream smoke condensates, but this finding on its own could not lead to ETS being classified as a Group 1 carcinogen. For the evidence that ETS causes lung cancer in humans to be considered sufficient IARC requires that a positive association be observed for which "a causal interpretation is considered to be credible" and for which "chance, bias or confounding" can "be ruled out with reasonable confidence."

The epidemiological data considered by IARC demonstrates that the risk of lung cancer in nonsmokers is associated with both spousal smoking and ETS exposure in the workplace. Since these associations are statistically significant, chance can be ruled out as an explanation with reasonable confidence. Since active smoking is the major risk factor for lung cancer in humans, and active smoking and ETS contain essentially the same smoke constituents (albeit at very different doses), a causal interpretation must be regarded as credible. It follows, therefore, that the conclusion that there is sufficient evidence that ETS causes lung cancer in humans (and hence that ETS is a Group 1 carcinogen) depends crucially on IARC's demonstration that bias and confounding can be ruled out with reasonable confidence.

Although IARC presents its own updated meta-analysis of the evidence relating ETS exposure to lung cancer risk in nonsmokers, these analyses are not adjusted for bias or confounding and merely serve to confirm the existence of an association. Instead, the conclusion that the excess risk "remains after controlling for some potential sources of bias and confounding" relies heavily on previously published meta-analyses of the evidence on spousal smoking and lung cancer in nonsmokers which have adjusted for bias due to misclassification of active smoking status and, in some cases, also dietary confounding and bias due to exposure to secondhand smoke other than the

spouse. The majority of these are old and based on limited data, the only two citations in the last 10 years being those of Hackshaw *et al* in 1997[1] and one[2] of our recently published series of five papers.[2-6]

As this series of five papers makes clear, the analyses of Hackshaw *et al* are open to considerable criticism, and do not support their conclusion, as IARC puts it, that "their overestimation due to misclassification bias and potential confounding seems to be balanced by the underestimation due to exposure to secondhand smoke in the reference group." However, IARC completely fails to address the points raised in our series of five papers, and indeed is guilty of misciting our work to such an extent that it appears to be claiming our findings are consistent with its view that any bias due to misclassification or confounding is small.

Thus, for bias due to misclassification of smoking, IARC appears to suggest that our analyses take no account of the fact that misclassified ever smokers are likely to have substantially less lung cancer risk than non-misclassified ever smokers, when of course they do so. Furthermore IARC fails to cite any of our misclassification adjusted estimates which, correctly take into account the well-documented much higher misclassification rate in Asian women. For confounding IARC selectively cites estimates of ours which minimize the effects of confounding, while ignoring others which show a greater effect. IARC also reiterates a claim made by Hackshaw *et al*[1] that those individual epidemiological studies which had attempted to adjust for confounding had generally shown the effect of adjustment was negligible, a claim discussed and shown to be misleading in our paper II.[4] IARC only cites one of our five papers at all (paper III[2]), and does not mention our paper V[6] which concludes that the association of spousal smoking with lung cancer risk in nonsmokers "essentially disappears" if proper adjustment is made for bias and confounding. IARC has presented no arguments whatsoever to argue against this conclusion. As such IARC clearly has <u>not</u> demonstrated that ETS causes lung cancer in humans, and therefore has not shown that involuntary smoking should be classified as a Group 1 carcinogen.

A considerable number of other comments are made in the text of this document. Some of the more important ones are listed below.

1. The Summary of the Monograph is, with very minor differences, the same as that released on the IARC website in 2002.
2. The style of the Monograph, while following that of previous Monographs, is open to criticism in not containing a section which explains how the Working Group has reached its evaluations based on the data evaluated. One example of this is for cancer of the nasal sinus, where the same evidence, regarded as demonstrating a causal relationship by the California EPA,[7] is not considered so by IARC, with no real explanation for the difference of opinion. While I would regard the conclusions of the California EPA as premature, in view of various weaknesses in the studies reporting an association of ETS exposure with nasal sinus cancer, IARC does not refer to any such weaknesses and it is not at all clear how the conclusions were reached.
3. In a number of areas where I am familiar with the literature, relevant studies (not published recently) are not cited.
4. Relative risks included in meta-analyses are not always appropriate, particularly for lung cancer and childhood ETS exposure.
5. Various sources of bias and confounding which might affect the data relating ETS exposure to lung cancer risk in nonsmokers (and relating to other associations) are not discussed at all.
6. IARC reiterates the claim of Hackshaw *et al*[1] that significant heterogeneity in the relative risk estimates for spousal smoking and lung cancer in nonsmokers can be explained by the results from one study in China,[8] without realizing that this is not actually true.[6] The fact that studies which do not adjust for age and studies which report dose-response results have substantially higher relative risks is never brought to light.
7. IARC's meta-analyses for childhood exposure are substantial overestimates, due partly to inclusion of results from some Asian studies (eg.[9]) which apparently

asked only about exposure from parents in adulthood, and partly to omission of relevant results from the IARC's own multicentre case-control study.[10]

8. IARC assumes that as active smoking causes lung cancer and as ETS involves exposure to substances similar to those present in tobacco smoke, some risk of lung cancer from ETS exposure will arise, without addressing alternative views to this no-threshold argument.

9. IARC correctly dismisses claims of an association between ETS and breast cancer, based on the complete lack of association seen in large, well conducted prospective studies.

10. IARC correctly argues that the evidence on ETS and childhood cancer is inconclusive.

11. IARC also correctly concludes that the evidence relating ETS exposure to cancer in adults of sites other than the lung (or breast) is inconclusive, though many of the relevant data are not cited.

12. IARC concludes that there is limited evidence in animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke. It considers data on lung tumour incidence in A/J and Swiss mice, the evaluation of the evidence as limited apparently being due to various doubts expressed about the appropriateness of the model.

13. Evaluation of the evidence in experimental animals for the carcinogenicity of sidestream smoke condensate as sufficient appears to be based only on one unsatisfactory skin painting study in mice,[11] and one rat lung implantation study involving fractions of sidestream smoke condensate.[12] The relevance of such studies to humans is unclear.

14. In its evaluation section, IARC gives prominence to there being "published reports on possible carcinogenic effects of secondhand smoke in household pet dogs." This is surprising given none of the risk estimates in the four studies cited[13-16] are statistically significant and the findings are not even consistently positive. The only companion animal study at all suggestive of a possible effect of ETS is actually in cats,[17] but even this is far from conclusive.

15. The Monograph includes a section on "Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms." Much of this concerns areas, such as genetic effects, on which I cannot usefully comment. It includes a subsection on ETS and coronary heart disease, which fails to make clear severe limitations in the epidemiological and experimental evidence, which I have discussed elsewhere,[18,19] and generally adds nothing new.

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INDEX

1. Background

1.1 The IARC Monograph Series

For some 30 years, the International Agency for Research on Cancer (IARC) has published monographs on the evaluation of the carcinogenic risk of chemicals to humans. Each monograph is prepared by a Working Group that is required to assess the evidence on humans, and on experimental animals, separately. For humans, there are four categories:

sufficient evidence of carcinogenicity – where a positive relationship has been observed in which chance, bias and confounding can be ruled out with reasonable confidence;

limited evidence of carcinogenicity – where there is a positive association, for which a causal interpretation is considered credible, but where chance, bias or confounding cannot be ruled out with reasonable confidence;

inadequate evidence of carcinogenicity – where the data on humans are non-existent or of too poor quality, consistency, or power, and

evidence suggesting lack of carcinogenicity – where there are several mutually consistent adequate studies showing no positive association.

The Working Group is also required to evaluate other data, such as that relevant to mechanisms of action. Based on all the evidence considered the Working Group also makes an overall evaluation of the agent as:

Group 1 : Carcinogenic to humans. This is used when the evidence for humans is sufficient or, exceptionally, when the evidence for humans is less than sufficient, but that for animals is sufficient and there is strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2A : Probably carcinogenic to humans. For this classification limited evidence in humans plus sufficient evidence in animals may be enough. Provided it is clear that the mechanism in animals also operates in humans, inadequate evidence in humans plus sufficient evidence in animals may also be enough in some cases. Also limited evidence in humans on its own may be enough on occasion.

Group 2B : Possibly carcinogenic to humans. This classification is used in three cases:

(i) limited evidence in humans and less than sufficient evidence in animals;

(ii) inadequate evidence in humans plus sufficient evidence in animals, or

(iii) inadequate evidence in humans plus limited evidence in animals plus supporting evidence from other data.

Group 3 : Not classifiable as to its carcinogenicity to humans. The main criterion here is inadequate evidence in humans plus inadequate or limited evidence in animals. An alternative criterion is where there is inadequate evidence in humans plus sufficient evidence in animals but strong evidence that the mechanism in animals does not apply to man.

Group 4 : Probably not carcinogenic to humans. This requires evidence of lack of carcinogenicity in animals plus normally evidence of lack of carcinogenicity in humans, though in some cases evidence of lack of carcinogenicity in animals plus supporting data may be enough.

The monographs have developed over the years from the joint efforts of many interested scientists, working within and outside IARC, with the intention of preparing reports in a consistent and balanced style.

The whole procedure has many strengths, but it is also evident that it has some general weaknesses. These strengths and weaknesses are described in detail elsewhere.[20] One weakness to which attention should be drawn is the lack of an explanation as to how a particular evaluation of carcinogenicity has been reached from the data presented. The monographs have the equivalent of 'results' and 'conclusions' sections of scientific papers, but often have no linking 'discussion' section. While the conclusions generally seem to flow logically from the results presented, there are exceptions, e.g. for cadmium in monograph 58.

1.2 IARC Monograph 38 (1986)

In 1986, in their volume 38 on tobacco smoking,[21] IARC briefly considered the evidence relating cancer to passive exposure to tobacco smoke. The section of that monograph on pages 303-308 made it quite clear that the epidemiological evidence available at that time was inadequate to incriminate ETS. For lung cancer IARC noted:

"Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, the risk of lung cancer in nonsmokers increased in relation to the extent of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke and to other possible risk factors for the various cancers studied. The resulting errors could arguably have artefactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk. As the estimated relative risks are low, the acquisition of further evidence bearing on the issue may require large-scale observational studies involving reliable measures of exposure both in childhood and in adult life."

IARC also noted that:

"Positive associations have been reported between passive exposure to tobacco smoke and cancers at all sites (Hirayama, 1984b; Sandler *et al.*, 1985a,b), for nasal sinus cancer and brain tumours (Hirayama, 1984b), and for cancers at many individual sites other than the lung (Sandler *et al.*, 1985a,b). The Working Group noted that these findings were at present difficult to interpret, as many related to sites that have not been strongly associated with active smoking."

and

"The studies on childhood cancer do not provide clear evidence as to whether or not there is a clear association with parental smoking."

Later in that monograph, however, IARC stated that though

"the observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk … knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer."

It is interesting to note that IARC's view, in 1986, that the epidemiological data on ETS and lung cancer provided unconvincing proof of a cause and effect relationship, conflicted with conclusions reached by the US Surgeon-General[22] and the US National Research Council[23] at about the same time.

1.3 Progress since 1986 and a change in views

Since 1986, the number of studies reporting results relating ETS exposure to cancer risk has increased dramatically, with by now over 60 studies of lung cancer available, as against only seven considered by IARC in Monograph 38.

Since 1986, IARC has devoted much effort to the assessment of risks associated with ETS exposure. Early work was methodological, attempting to validate the use of questionnaire indices of exposure based on self-report by more objective estimates of tobacco smoke uptake based on cotinine. Results of a study conducted in nonsmoking women conducted in 13 centres in 10 countries in North America, Europe and Asia were published in 1990,[24] the data later being used to attempt to quantify the extent to which smokers deny smoking.[25]

This study was the prelude to the IARC West European multicentre lung cancer case-control study, conducted in 12 centres in seven countries, and reported in detail in a paper in the Journal of the National Cancer Institute[26] and in an associated IARC Technical Report.[10] Although large, involving a total of 650 lung cancer cases and 1542 controls who had either never smoked or smoked very little, and so capable of detecting a moderate association as statistically significant, the study found no significant increase in lung cancer risk associated with ETS exposure from various sources (spouse, other cohabitants, workplace, vehicles, other indoor settings, childhood) in either sex or in males and females combined. There was some weak evidence of a positive dose-relationship with spousal and workplace exposure and of a negative dose-relationship with childhood exposure.

Over the period from 1986, IARC staff and associated scientists have also published numerous review papers which led them to a view which emerged in the 1990s that the carcinogenicity of ETS is "well established." Elsewhere, in 1998, my colleague Alison Thornton and I[20] critically examined the content of these papers. We found them

"to contain numerous limitations, including failure to report results using standardized indices of ETS exposure, failure to show weakening of the association over time, failure to make it clear the association with lung cancer is only for spousal smoking and does not apply for workplace exposure, failure to investigate sources of between-study heterogeneity, failure to consider study quality adequately, failure to consider histological type, seriously inadequate consideration of sources of bias, overstatement of biologic plausibility, and inadequate consideration of proof of causation."

We also noted that

"the strength of the epidemiological evidence relating ETS to lung cancer appears to be less than that for all other agents classified by IARC as having 'sufficient' evidence of carcinogenicity, and is no stronger than that for various agents with a 'limited' classification. 'Limited' evidence of carcinogenicity would appear a more appropriate classification for ETS."

Since 1986, many reviews of the evidence on ETS have been published. Politically perhaps the most important have been those by the EPA in 1993,[27] by OSHA in 1994,[28] by the Australian National Health and Medical Research Council in 1997[29] and by the Californian EPA in 1999,[7] as well as the review papers in 1998 on lung cancer by Hackshaw, Law and Wald[1] and on heart disease by Law, Morris and Wald.[30]. Although the establishment medical opinion is that the association of ETS with lung cancer and heart disease cannot be explained by the various potential biases involved, this view has been challenged, both by Robert Nilsson[31,32] and by myself and my colleagues, notably in a recently published series of five papers on ETS and lung cancer [2-6] specifically aimed at refuting the conclusions of Hackshaw et al.[1] These five papers will usually be referred to subsequently as 'our paper I', 'our paper II' etc. when citing them individually, or as 'our series of five papers' when citing them collectively.

1.4 Pre-release of the conclusions of a new Monograph in 2002

In mid 2002 considerable media attention was given to a press release by WHO/IARC claiming that it had now been conclusively demonstrated that ETS was carcinogenic. Reading between the lines, it appeared that IARC had recently prepared a new monograph. On 11th July 2002 I wrote to Dr Paulo Boffetta of IARC whom I know and who was first author of the paper on the West European multicentre case-control study.[26] I asked him if he would be kind enough to send me a copy of the monograph, even if in pre-publication state, as ETS was a special interest of mine and I had published widely on it. I sent him reprints of our series of five papers[2-6] I also expressed some surprise that I had not been

invited to be a member of the working group, given my involvement in previous IARC publications and my extensive publications on ETS.

Boffetta replied on 30th August 2002, pointing out that there was a summary of the Monograph on the IARC website, that the full text would be available in about one year's time, and that their policy was not to provide copies of the draft document. He also noted that they had not invited scientists with links with the tobacco industry as members of the Working Group for the Monograph "because of recent attempts by the tobacco industry to undermine the work of WHO and IARC." However Boffetta assured me that the Group had considered all the relevant literature, including those studies financially supported by the tobacco industry. He did not comment on our series of five papers.[2-6]

Before Boffetta replied I had already become aware of the existence of the summary of the Monograph (Monograph 83) and on 1st August 2002 I had prepared some comments on this material in advance of publication of the full monograph.[33]

1.5 IARC Monograph 83 finally appears

Over the next two years I looked out at intervals for the appearance of Monograph 83, and around the beginning of June 2004 (about two years after the appearance of the summary) it became clear that it was available. A copy finally reached my office on 17th June.

It consists of 1452 pages entitled 'Tobacco Smoke and Involuntary Smoking.' The main sections include:

Pages 3-6. List of participants This includes the 25 members of the working group, which met on 11th to 18th June 2002. Many of these are household names in the literature on smoking or ETS and health, including Sir Richard Doll, Sir

Richard Peto, Elizabeth Fontham, Jonathan Samet and Michael Thun. Only two names – David de Marini and Gary Stoner – are not known to me. The list also includes 21 members of the IARC Secretariat (including Paulo Boffetta), 3 observers and 11 others who provided assistance.

Pages 9-31. Preamble This describes how the Monographs programme works, and appears in all the Monographs. I have already summarized some of the main features of this in section 1.1 above.

Pages 33-47. General remarks This is predominantly an attempt to summarize the magnitude of the effect of active smoking on health, reiterating material published elsewhere by Doll and Peto, and does not really concern ETS. It also includes a section on "methodological considerations in interpreting epidemiological evidence on smoking and disease."

Pages 51-1187. Tobacco Smoking I will consider this part of the Monograph, dealing with active smoking, elsewhere. I note that the 2004 Surgeon General's Report became available at the same time as Monograph 86. This Report only considers active smoking and I will consider this Report when I consider the active smoking part of Monograph 83.

Pages 1189-1413. Involuntary Smoking This is the focus of my present review. Pages 1409-1413 contain the "summary of data reported and evaluation" which, apart from some very small differences that I will mention later, is identical to that published in 2002.

Note that my review of the section on Involuntary Smoking is an expansion of that prepared based on the summary in August 2002.[33] Some sections of text appearing in 2002 are repeated here for convenience.

2. Evaluation of involuntary smoking by the IARC

The section on involuntary smoking ends on page 1413 with the following, identical to that in the 2002 Summary:

"**5.5 Evaluation**

There is *sufficient evidence* that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans.

"There is *limited evidence* in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke."

"There is *sufficient evidence* in experimental animals for the carcinogenicity of sidestream smoke condensates."

"In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs."

"**Overall evaluation**

Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is *carcinogenic to humans (Group 1).*"

The IARC overall evaluation as Group 1 derives from the fact that it regards the evidence in humans as sufficient, its rules not requiring any evidence in animals in order to make this evaluation. Had the human evidence been regarded as limited (a position I will defend later), a Group 1 classification would not have been reached, and IARC would have to make an overall evaluation of Group 2. Whether the appropriate classification would then have been Group 2A (Probably carcinogenic to humans) or Group 2B (Possibly carcinogenic to humans) is not clear. As noted earlier, a Group 2A classification normally requires limited evidence in humans and sufficient evidence in animals, provided it is clear that the mechanism in animals also operates in humans. However,

IARC states that, exceptionally, limited evidence in humans may on occasion be enough for a Group 2A classification, and may regard limited evidence for ETS coupled with sufficient evidence for active smoking as compelling.

One point to be borne in mind with the whole IARC process is that it implicitly accepts the dubious no-threshold argument, the statement that an agent is carcinogenic being made without any reference to the extent of exposure. This is clearly a severe limitation of the process (see section 4.12 of these comments).

3. Areas considered in this commentary

It is clear from the above that the evaluation of the human evidence is fundamental to the Group 1 evaluation. It is also clear, both from the first paragraph of the evaluation section, and from the section of the summary on human carcinogenicity data (5.2, pages 1409-1411) that the sufficient evidence of causality in humans relates only to lung cancer. Therefore I first, in section 4 of this commentary, consider in detail the evidence IARC present in relation to lung cancer. I then follow, in sections 5 to 7, with briefer commentaries on the three other areas IARC consider in relation to human carcinogenicity, breast cancer, childhood cancer and other cancer sites. Then, in sections 8 to 10, I consider in turn the three other areas highlighted in IARC's evaluation, carcinogenicity of mixtures of mainstream and sidestream tobacco smoke in animals, carcinogenicity of sidestream smoke condensates in animals and effects of household pets. In section 11, I comment on various other areas in the Monograph on involuntary smoking. Finally, in section 12, I summarize my overall comments.

4. Lung cancer

4.1 Basis for the claim that ETS causes lung cancer in humans

Support for the view that there is "sufficient evidence" that involuntary smoking causes lung cancer in humans comes from the following text in section 5.2 of the summary:

"Involuntary smoking involves exposure to the same numerous carcinogens and toxic substances that are present in tobacco smoke produced by active smoking, which is the principal cause of lung cancer. As noted in the previous *IARC Monograph* on tobacco smoking,* this implies that there will be some risk of lung cancer from exposure to secondhand tobacco smoke.

"More than 50 studies of involuntary smoking and lung cancer risk in never smokers, especially spouses of smokers, have been published during the last 25 years. These studies have been carried out in many countries. Most showed an increased risk, especially for persons with higher exposures. To evaluate the information collectively, in particular from those studies with a limited number of cases, meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together. These meta-analyses show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk is of** the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Furthermore, other published meta-analyses of lung cancer in never smokers exposed to secondhand tobacco smoke at the workplace have found a statistically significant increased risk of 12-19%†. This evidence is sufficient to conclude that involuntary smoking is a

* "1986 IARC Monograph on Tobacco Smoking" in the 2002 Summary
** "on" rather than "of" in the 2002 Summary
† "16 to 19 per cent" in the 2002 Summary

cause of lung cancer in never smokers. The magnitudes of the observed risks are reasonably consistent with predictions based on studies of active smoking in many populations."

Fuller support for the views expressed in the summary is presented in section 2.1 (pages 1231-1271). This includes 10 tables (Tables 2.1-2.10) as follows:

(a) Two tables which describe the details of the relevant studies:
prospective (cohort) studies (Table 2.1, pages 1232-1233) and
case-control studies (Table 2.3, pages 1238-1253);

(b) Four tables which present relevant relative risk estimates:
spousal exposure (Table 2.2, pages 1234-1236)
highest spousal exposure (Table 2.4, pages 1255-1256)
workplace exposure (Table 2.5, page 1258) and
childhood exposure (Table 2.6, page 1260);

(c) Three tables which present results of various published meta-analyses:
spousal exposure (Table 2.7, page 1265)
workplace exposure (Table 2.8, page 1266) and
childhood exposure (Table 2.9, page 1267); and

(d) A final table which summarizes updated meta-analyses for spousal, workplace and childhood exposure (Table 2.10, page 1270).

Following a brief introductory section, sections of the text are as follows:

2.1.1 Cohort studies (page 1231)

2.1.2 Case-control studies (page 1237)

(a) Description of studies (page 1237)

(b) Exposure to secondhand smoke from the partner (page 1254)

(c) Exposure to secondhand smoke at the workplace (page 1257)

(d) Exposure during childhood (page 1259)

(e) Exposure from other sources (page 1259)

(f) Bias and confounding (page 1261)

2.1.3 Meta-analyses of observational studies of exposure to secondhand smoke and lung cancer in adults (page 1263)

(a) Introduction (page 1263)

(b) Published meta-analyses (page 1264)

(c) Updated meta-analyses (page 1269)

The structure is slightly strange as although section 2.1.2(a) relates to case-control studies, many of the further sub-sections of 2.1.2 clearly relate to both cohort and case-control studies.

4.2 Introduction to my comments on ETS and lung cancer

In the paragraphs that follow I discuss in some detail a number of aspects of the material and arguments relating to ETS and lung cancer which are presented in the Monograph in section 2.1 and summarized in section 5.2. I first discuss whether all the relevant studies have been cited, then consider whether the relative risks included are appropriate, and then look in turn at the various issues relating to interpretation of the data, including sources of bias and confounding. I next consider the validity of the various meta-analysis estimates of risk presented, and then consider some issues not covered in section 2.1, which are alluded to in section 5.2. I then consider whether, in my view, IARC has demonstrated that ETS causes lung cancer in humans.

In my considerations I make a number of references to the series of five papers, 'Revisiting the Association between Environmental Tobacco Smoke Exposure and Lung Cancer Risk,'[2-6] which I and my colleagues John Fry and Barbara Forey prepared partly in reply to the review paper by Hackshaw, Law and Wald.[1] I also refer to data in the reviews I routinely update annually for the TMA.[34-36] It should be noted that only one of the series of five papers[2] is cited in the references to section 2 of the Monograph.

4.3 Are all the relevant studies cited?

Table 2.1 cites eight prospective studies. Of these, one[37] is actually a case-control study nested within a prospective study, though as the exposure was determined before onset of disease, it is reasonable for IARC to include it here. Two prospective studies are omitted. One, published in 1989,[38] is based on only nine lung cancer deaths in nonsmokers so its omission is unimportant. Interestingly it is referred to in the footnote to Table 2.2 as providing data for men and women combined. The other, the well known Enstrom and Kabat study[39] was not published until 2003 so was presumably too late for consideration – I note that studies after 2001 are generally not included.

Table 2.3 cites around 50 studies. Some of these are subsets of the Boffetta multicentre study[26] and results are not included in the tables of relative risks. Generally the coverage was reasonably complete up to 2000, though there are some omissions.[40-45] Some of these may have been because they were not published in peer-reviewed journals. There are a few other more recent papers available that provide relevant data.[46-50]

I would not expect these omissions to make any material difference to the overall interpretation of the data.

4.4 Are the appropriate relative risks included?

The data in Tables 2.2 (spouse), 2.5 (workplace) and 2.6 (children) can be compared with those in my current TMA Summary,[34] while the dose-response data in Table 2.4 (spouse) can be compared with that in the first paper in our series of five papers.[3]

Correspondence cannot be checked exactly, as the IARC tables only give data to one decimal place – unsatisfactory as it imparts a considerable imprecision, particularly to estimates or lower confidence levels which are

substantially below one. For example, a confidence limit given as 0.1 might actually be 0.051 or 0.149, values which vary by a factor of about 3.

Spousal data (Table 2.2)

Comparison with my own data revealed only a handful of material points:

1. Previously unpublished data from the Kreuzer study in Germany[51] of 0.8 (95% CI 0.5-1.3) for women and 0.4 (0.1-3.0) for men are presented in Table 2.2. These relative risks were specially calculated by Kreuzer so as to exclude those cases and controls already included in the Boffetta multicentre study.[26] The data presented in the original paper[51] would have had considerable overlap with the Boffetta data[26], and I had excluded them from my meta-analyses because of this. I will include these new estimates when next I update my database.
2. For the study by Shen *et al*[52] the adjusted relative risk which IARC gives for women is 1.6 (0.7-3.9) whereas I give an estimate of 0.75 (0.31-0.78). Their estimate comes from Table II of the source paper which is completely inconsistent with the data in Tables III and IV, which are consistent and which I used for my calculations.
3. For the study by Jee *et al*[53] IARC cites an adjusted relative risk of 1.9 (1.0-3.5) whereas I give an estimate of 1.72 (0.93-3.18). This is because the IARC estimate is for 'spouse current smoker,' whereas mine is for 'spouse ever smoker.' In other studies it has been usual to select data with 'spouse ever smoker' as the exposure index wherever there is a choice, as 'spouse ever smoker' is the index for which data are more commonly presented.

There are other minor differences, but none are material. As in our comparison with the Hackshaw data,[2] differences in the actual relative risks cited for spousal smoking are probably unlikely to have any real effect on the inferences to be drawn, though this is considered further in section 4.11.

Workplace data (Table 2.5)

There are a few points to note here:

1. Data are not presented from the large US Cardenas and Brownson 2 studies.[54,55] In the original publications the studies reported only that they had found no association, but relative risks were later reported by W J Butler[56] in a submission to OSHA. The resulting estimates are close to 1 and have quite large weight – Brownson study 0.98 (0.74-1.31) for females, and Cardenas study 1.09 (0.62-1.91) for males and 1.00 (0.65-1.54) for females.
2. Data are not presented from the large US Janerich study[57] which reported a risk estimate of 0.91 (0.61-1.35) per 150 person-years exposure.
3. Differences between the IARC estimate of 1.4 (0.8-2.5) and mine of 1.7 (0.69-4.18) for the Kalandidi study[58] depend on whether exposed = 'minimal' + 'some' and unexposed = 'housewife' (IARC) or exposed = 'some' and unexposed = 'minimal' (Lee). It seems appropriate to exclude those who do not work from workplace analyses.
4. For the second Boffetta study[59] I used the adjusted estimate of 1.5 (0.8-3.0) given in Table IV of the same paper. The IARC estimate of 1.0 (0.5-1.8) is, according to the source paper, that for spousal exposure.
5. As for spousal data, there are relevant new data reported for the Kreuzer study.[51]

Clearly omitting the data from the three large US studies[54,55,57] will have led to some overestimation of the effect of workplace exposure.

Childhood data (Table 2.6)

Comparing the estimates in Table 2.6 (which are where possible unadjusted for covariates) with those in my database, one major main difference I note is that IARC presents, but I do not, estimates for five studies. One is the Kreuzer study,[51] for reasons discussed already. The other four are studies by Shimizu,[9] Wu-Williams,[8] Stockwell[60] and Sun.[61] In my view the Shimizu,

Stockwell and Wu-Williams data should not have been included as the data seem to relate to parental exposure in adulthood not childhood, as is the case for the maternal and paternal exposure results for the Sun study. It is also surprising that, for the Boffetta multicentre study,[26] Table 2.6 fails to include sex-specific data available relating to exposure from the mother and father in childhood (see section 4.11 of my comments for further details).

Data for other sources (Text page 1259)

Apart from citing a single estimate from one study[51] reporting a significantly increased risk for exposure in vehicles in the highest category of weighted duration of exposure, no data are presented in relation to other sources, including social exposure, exposure in travel and total exposure. On my database[36] I have estimates from 8 studies for social exposure, 5 studies for exposure in travel and 20 studies for total exposure. Although the data are more numerous than IARC indicates, assessment of the evidence based only on the results for spousal, workplace and childhood exposure seems, however, not unreasonable.

Dose-response data for spouse (Table 2.4)

The data in Table 2.4 are for the highest exposure level reported in the study. Clearly this does not provide full information about the dose-response relationship. I have not conducted a detailed check of all the data but it is clear that most of them are correct and correlate highly with the data presented in Tables 1 and 2 of paper I of my series.[3] I do note, however, that IARC has continued to include the narrow confidence intervals for the data in the Geng study,[62] shown to be erroneous elsewhere[63] in a paper describing 'Simple methods for checking for possible errors in reported odds ratios, relative risks and confidence intervals.' I note also that the confidence intervals for the data for cigs/day from the Akiba study,[64] which are noted to be estimated by IARC, are clearly also far too narrow. The relative risk estimate of 2.1 is given as having a 95% CI of 1.7-2.6, which would imply a very high level of statistical significance.

According to our own estimates[3] the 95% CI should be 0.57-8.07, implying the increase is not actually significant at all. An error has also been made with the 95% CI for the estimate for the Inoue and Hirayama study,[65] where the reported relative risk of 3.4 is not statistically significant, as IARC indicate it is.

Though a number of the relative risk estimates for high exposure (in terms of cigs/day) are statistically significant, none are highly significant, as would be suggested by the erroneous Akiba and Geng estimates.

Other dose-response data (Text pages 1257 and 1259)

I have not attempted, at this stage, to check the accuracy and completeness of the dose-response data on workplace or childhood exposure reported in the text of pages 1257 and 1259. The dose-response data for childhood exposure are extremely limited.

4.5 Misclassification bias

On pp 1262-1263, there is a discussion about misclassification bias (due to some current or former smokers being recorded as never smokers). The explanation of the mechanism behind the bias is correct, as is the statement that there are four major determinants of it – the prevalence of smoking in the population; the aggregation (or concordance) ratio; the relative risk of lung cancer in misclassified ever smokers; and the proportion of ever smokers misclassified as never smokers. However, there are two glaring weaknesses in the section.

The first is the statement:

"Some meta-analyses have assumed that the risk for lung cancer in misclassified smokers is the same as that in all reported smokers (US Environmental Protection Agency, 1992; Lee 1992, 1998)."

This implies to the reader that this is what the EPA and I thought. Nothing could be further from the truth. Wells (for the EPA) and I were both very well

aware that, as IARC explains, "misclassified current smokers tend to be light smokers and misclassified former smokers have usually given up smoking many years before the study," and our meta-analyses specifically took this into account. Did IARC really think we had our methods for misclassification adjustment so fundamentally wrong?

The second relates to the discussion in the next paragraph entitled "the percentage of current and former smokers misclassified as never smokers." This discussion is extremely superficial for various reasons:

(a) It does not actually discuss at all how the percentage of former smokers misclassified as never smokers is estimated. All the discussion relates to comparing self-reported smoking status with cotinine levels, which relates only to misclassification of current smoking;

(b) No reference is made to the considerable data showing very high misclassification rates of current smoking in Asian women[66]; and

(c) No reference is made to the extensive data on misclassification reviewed by Barbara Forey and myself.[67]

The discussion at this stage of the Monograph is theoretical. The effect that IARC judges misclassification to have on meta-analysis estimates is not considered at this stage. The issue is considered further when they present their meta-analyses (see section 4.11 of my comments).

4.6 Bias resulting from exposure to secondhand smoke in the reference group

This section consists of three sentences:

"Studies of the risk for lung cancer and exposure to secondhand smoke have defined the reference groups as never-smoking women with husbands who are nonsmokers. However, these women, although not exposed at home, may be exposed to secondhand smoke outside

the home. This bias will tend to underestimate the true relative risk."

The first two sentences are fine, but the last sentence involves two problems. One, it does not mention that the bias will only occur if indeed ETS does have a true effect. Thus, if one can demonstrate that the whole of the increase in risk associated with marriage to a smoker can be explained by bias and confounding, this bias becomes irrelevant. Second, it is not clear what risk one is talking about in this sentence. Presumably, IARC means the increase in risk of lung cancer in nonsmoking women with a smoking husband relative to that of a nonsmoking women with no ETS exposure at all, i.e. the risk associated with an ETS dose greater than that from a smoking husband. In some ways, this is an odd concept.

4.7 Dietary confounding

The paragraph on p 1263 is open to criticism on a number of counts:

(i) IARC only considers confounding by diet, when other sources of confounding may be relevant. In our paper II[4] we also considered in detail the confounding effects of dietary fat and education, and we noted that social class, income and occupational exposure to specific lung carcinogens might also confound, though relevant data to do the adjustment are much sparser. Also, in our paper IV,[5] we show that failure to adjust for age in some studies may also have caused bias, since risk estimates for spousal smoking were much higher in those 11 studies that failed to adjust for age.

(ii) Having headed the section "dietary confounding," IARC considers fruit and vegetable consumption as the only relevant source of confounding.

(iii) The paragraph includes a sentence, "None of these potential confounders have been established as having a causal link with lung cancer" which, even if true (which is difficult to tell as

"these potential confounders" is not defined) is irrelevant. I had lengthy discussions with Jonathan Samet 10 years ago, trying to disabuse him of the totally unsound notion that one had to have demonstrated that a risk factor caused the disease before one could adjust for it in analysis.

(iv) The paragraph includes a statement stating that those studies which had attempted to adjust had generally shown the effect of adjustment was negligible. This is a myth which appeared earlier in the Hackshaw paper[1]. As John Fry and I conclude in our paper II,[4] following a detailed look at the evidence:

"Overall, the evidence available on confounding from epidemiological studies of ETS and lung cancer must be considered of very limited value. It is clear that it does not rule out the possibility of moderate confounding by fruit, vegetables, dietary fat or education."

(v) Another criticism that can be made of this section is that no mention is made of our paper II,[4] which considers the whole issue of the role of confounding in such depth.

4.8 Publication bias

The discussion of this on pages 1268-1269 correctly explains how publication bias works and notes the difficulty of assessing it. However, it contains some misleading statements. Firstly, it reiterates an old chestnut about there needing to be about 300 unpublished studies to explain the increased risk observed, without making the vital point that this is only if one wants to explain the whole of the observed increase in terms of publication bias, which is hardly likely. Publication bias could be just one source of bias among others.

Second, citing the work of Copas and Shi,[68] IARC states that it "assumed that 40% of all studies are unpublished." But Copas and Shi did not assume that; they merely presented a table showing how, using its methodology,

the magnitude of the publication bias depended on the proportion of published studies. Actually the cited reduction in the risk estimate from 1.24 to 1.15 as a result of correcting for publication bias, as cited by IARC, relates to a publication probability of 80%, i.e. if 20% not 40% of all studies are unpublished.

Finally, the next sentence, "Even with such an extreme assumption, the adjusted estimate is consistent with the reported relative risk adjusted for bias and confounding (1.26; 95% CI, 1.06-1.47)" seems to have no merit at all. If correcting for one source of bias produces a similar relative risk estimate to correcting for another source of bias, this does not mean that correcting for both would not produce a much lower relative risk estimate.

4.9 Sources of bias not considered

The biases considered in sections 4.5-4.8 above are the only ones IARC refers to. There are, however, a number of sources of biases that are, or may be, relevant. These are all discussed in our paper V.[6] These include recall bias, bias due to diagnostic inaccuracy, bias due to systematic differences in data collection methods between cases and controls in some studies, and bias due to errors in determining ETS exposure.

Also, as clearly demonstrated in our paper I,[3] an important source of bias arises when assessing the dose-response evidence. It is abundantly clear that simple exposed/unexposed relative risk estimates tend to be markedly higher for those studies that do present dose-response data than for those studies that do not. IARC are remiss in failing to point out the clear consequence of this, namely that Tables such as Table 2.4 give a markedly misleading impression of the strength of the dose-response evidence.

Also missing from the Monograph is any reference to the fact that dose-response analyses are subject to much the same sorts of bias and confounding as

are simple exposed/unexposed comparisons. Thus, for example, misclassification bias and confounding, as well as publication bias, will affect estimates of the risk of lung cancer per 10 cigarettes smoked.[2-4]

4.10 Some statistical issues

On page 1267, it is noted that similar answers are given by fixed or random effects meta-analysis and also by Bayesian and the usual frequentist analyses. The first statement is certainly true in my experience and I believe the second is also true. It is the magnitude of the biases that is important, rather than what answer one might get by various means of combining the data.

On page 1269, there is a discussion of heterogeneity. IARC follows Hackshaw in claiming that those sources of heterogeneity in the spousal smoking risk which I identified in a paper published in 1998,[69] such as variation in relative risk by region, publication date, study type and study size, were all due to the effect of a single aberrant study in China with a low relative risk estimate.[8] A more recent analysis in our paper IV[5] tends to argue against this view. As is shown in this paper, there are clear sources of heterogeneity other than the study in China, in particular in relation to whether or not the study age adjusted or reported dose-response results for smoking by the husband. There is also evidence that risk estimates tend to be lower in large studies, in studies published in the 1990s, in studies not requiring histological confirmation of all cases, and in studies where the proportion of proxy respondents was no higher in cases than in controls, though these associations are not independent. Variations in risk by study characteristics actually largely explain the apparently low relative risk in the study in China,[8] arguing against the view that it is an outlier, and therefore should perhaps be excluded from meta-analyses.

4.11 Overall relative risk estimates

For each of the three main ETS exposure indices (spouse, workplace and childhood), results are presented firstly of a number of published meta-analyses

and then of an updated meta-analysis that IARC itself has conducted. The updated meta-analysis is based on the data included in Tables 2.2, 2.5 and 2.6. As described on page 1269, random effects meta-analysis has been used based on crude (unadjusted) rather than adjusted relative risk estimates. In my experience, there is usually not a marked difference between estimates that are based on fixed-effects or on random-effects analysis. Nor is there much difference between overall estimates using crude relative risks where possible and estimates using adjusted relative risks where possible. As I have very comparable analyses available[36] based on the latest data, I will compare my findings with those given by IARC in Table 2.10.

It is important to note that the updated meta-analyses are not adjusted for misclassification bias. Nor are they adjusted for potential confounding by fruit, vegetables, dietary fat and education, as was the case in the analyses we have presented in paper II.[4] Nor are they corrected for background ETS exposure of the reference group.[1] They should be seen only as estimates of the magnitude of the association between lung cancer risk in nonsmokers and ETS exposure from the various sources. Correction for some or all of these sources of bias is only considered in the published spousal meta-analyses (see Table 2.7 and page 1264).

Spousal exposure

Table 2.7 summarizes published meta-analysis results from 11 papers. For each of these papers there is a pooled relative risk estimate, which is the estimate before adjustment for misclassification bias, dietary confounding and background ETS exposure. For some of the papers IARC presents estimates adjusted for one or more of these factors. Many of these estimates are historic, e.g. the Wald paper in 1986[70] or the EPA report.[27] Of more recent estimates, the only ones that have adjusted for any of the three sources of bias are the Hackshaw analysis[1,71] and our own work, where only paper III[2] of our series of five papers is cited.

It should be noted that the citation by IARC in Table 2.7 of findings from our paper III[2] merely relates to analyses correcting exposed/unexposed spousal relative risk estimates for misclassification only. The unadjusted relative risk, based on 47 estimates for women, is correctly cited as 1.23 (1.12-1.36), and the relative risk adjusted for misclassification is cited as 1.17. However, the estimate of 1.17 is based on the Hackshaw method for adjustment and not on the Lee and Forey method advocated in our paper. It also assumes that misclassification rates in Asian populations are no greater than in Western populations, which considerable evidence shows not to be the case.[66] In our paper III[2] a table is presented showing how the corrected estimate declines with increasing assumed values of the misclassification rate. For a misclassification rate of 20% in Asia and 2.5% in Western populations, which is quite plausible, the corrected value would be 1.10 (0.97-1.24), i.e. misclassification on its own might well explain about half of the observed association.

IARC does not include our estimates adjusted for confounding in Table 2.7, since they relate to the estimated increase in risk per 10 cigarettes smoked per day by the husband and not to the simple exposed/unexposed relative risk with which Table 2.7 is concerned. However, IARC does discuss these analyses in the text on page 1264. It notes that the relative risk of lung cancer per 10 cigs/day smoked by the husband was reduced from 1.10 to 1.09 after adjustment for fruit, vegetables, dietary fat and education, a correction which is small.

Why does IARC only cite a confounder-adjusted estimate of 1.09? In our paper II[4] John Fry and I were at pains to discuss the problem caused by one of the studies we used to assess the association between ETS and confounding variables being very large, and finding ETS exposure to be associated with <u>reduced</u> dietary fat consumption and, in males, with <u>increased</u> years of education, associations which were unexpected and in the opposite direction to those seen in the other studies. A question arose as to how to combine the evidence from the different studies. One approach ('weighted means') allowed the large study to dominate the

overall evidence on the association between ETS and dietary fat or education and did indeed lead to the results IARC cited, but an alternative and arguably more appropriate approach ('unweighted means') led to a confounder adjusted relative risk per 10 cigs/day smoked by the husband of 1.06. IARC was clearly seriously misleading in not mentioning this estimate.

IARC did not mention results we cited relating to simultaneous adjustment for misclassification and confounding. Hackshaw[1] had originally estimated that risk of lung cancer in nonsmokers increased by 23% per 10 cigs/day smoked by the husband. We found[6] that

"The estimated increase essentially disappears if proper adjustment is made for smoking misclassification bias, if correction is made for the joint effects of confounding by fruit, vegetables, dietary fat and education, if errors in published data in one study are corrected, and if results from all pertinent studies are included (and not just those which report risk by level of smoking by the husband). Taking account of all these factors and using unweighted estimated of the association between ETS exposure and the confounding variables (as one very large study reported results discrepant from those for numerous smaller studies), the risk increase per 10 cigarettes/day was found to be 2% (95% CI -3 to 7.5%), based on data from 47 ETS/lung cancer studies. Using weighted estimates, the risk increase was 5.5% (95% CI 0 to +11%)."

IARC fails to mention the results of these analyses, although it cites our paper III[2] from which the adjusted relative risk estimates were derived. Instead IARC merely cites highly selected results from our paper III that give a false impression that bias due to misclassification and confounding is minimal. It also fails to cite our paper V[6] which considered the effect of restricting attention to those studies that adjusted for age. When this was done the adjusted estimate of +2% using unweighted estimates cited in the previous paragraph reduced to –2%

(95% CI –6 to +3%), while the estimate of +5.5% using weighted estimates reduced to +1% (95% CI –4 to +6%).

The section on pages 1265-1266 ends with a statement that

"Generally, the overestimation due to misclassification bias and potential confounding seems to be balanced by the underestimation due to exposure to secondhand smoke in the reference group (Hackshaw *et al.*, (1997)."

This may have been true in Hackshaw's analysis but is certainly not true in ours. As we point out in our paper V,[6] such adjustment should theoretically only be applied if a true statistically significant increase has been demonstrated, which is not the case. Even if it is applied, it only has a small effect – for example, the estimate of a 2.1% increase per 10 cigs/day smoked by the spouse using unweighted estimates (and not excluding studies that failed to age adjust) would only become 3.2% (and still not be statistically significant) if adjustment for ETS exposure in the reference group is made.

In its updated meta-analyses in Table 2.10 IARC cites these results:

Sex	Studies	Pooled relative risk (95% CI)	Evidence of heterogeneity
Female	46	1.24 (1.14-1.34)*	No, p=0.08
Male	11	1.37 (1.02-1.83)	No, p=0.80

* 1.27, 1.15-1.41 using adjusted relative risks where available

These are based on the data in Table 2.2, page 1234, using crude relative risks where available and random-effects meta-analysis. Comparable results from my most recent meta-analyses[36] are as follows:

Sex	Studies	Pooled relative risk (95% CI)	Evidence of heterogeneity
Female	62	1.21 (1.12-1.30)	Yes, $p<0.05$
Male	21	1.15 (0.97-1.35)	No, $p\geq0.1$

The results for females are reasonably comparable to those IARC gives, but my estimates for males are substantially lower. For the 11 studies that IARC cites, the data are identical in 9, and the main reason why my estimates are lower is that data are included for 10 additional studies.

Below I give some additional relative risk estimates from my analyses:

		Choosing crude data for preference		Choosing adjusted data for preference	
Sex	Studies	Fixed effects	Random effects*	Fixed effects	Random effects
Female	62	1.18	1.21	1.17	1.22
Male	21	1.15	1.15	1.13	1.13

* Comparable to the updated meta-analyses IARC presents in Table 2.10

It is clear the overall estimates are not materially affected by the way the meta-analysis is conducted. In the accompanying text (on page 1269), IARC notes that "the risk estimates for both nonsmoking men and women are statistically significant." In fact, only that for women is, using the latest data, but this does not affect the conclusion that there is a significant association of spousal smoking with lung cancer risk in nonsmokers. The relevant issue is whether the association can or cannot be explained by bias and confounding.

Exposure at the workplace

On page 1266 and in Table 2.8 IARC presents the results of various previously published meta-analyses relating to spousal exposure. Only the most recent analyses, by Wells[72] and by Zhong[73] report a significant association. The analysis by Wells was, unusually, restricted to studies that were based on self-reported exposure. IARC concludes that

"Overall, there seems to be an increased risk of lung cancer in subjects exposed to secondhand smoke at the workplace."

In their updated meta-analyses in Table 2.10 based on the data in Table 2.5, page 1258, IARC cites the following results:

Sex	Studies	Pooled relative risk (95% CI)	Evidence of heterogeneity
Female	19	1.19 (1.09-1.30)*	No, p=0.87
Male	6	1.12 (0.80-1.56)	No, p=0.38
Both	7	1.03 (0.86-1.23)	No, p=0.10

* 1.21, 1.09-1.35 using adjusted relative risks where available

Note that none of the published or updated meta-analyses for workplace exposure are adjusted for misclassification bias or confounding, a point not made very clear by IARC. As discussed in our paper V,[6] there is evidence that smokers tend to work with smokers, so that misclassification bias would tend to operate in a manner similar to that for spousal smoking (where smokers tend to be married to smokers). Other sources of bias may also operate, such as recall bias and publication bias.[6]

Our own analyses[36] which pool together results for males, females and sexes combined, give a relative risk, based on 30 estimates, of 1.20 (1.11-1.30) using unadjusted relative risks where available and 1.21 (1.11-1.31) using covariate adjusted relative risks where available.

Thus we agree that there is an association, which is statistically significant. However, again issues of confounding and bias mean that one cannot readily interpret the association as a causal one.

Exposure in childhood

On pages 1266-1267 and in Table 2.9 IARC presents the results of three published meta-analyses, none of which report a significant association. Indeed all the relative risk estimates are slightly below 1.0.

In their updated meta-analyses in Table 2.10, based on the data in Table 2.6, pages 1260-1261, IARC cites the following results:

Source of exposure	Sex	Studies	Pooled relative risk (95% CI)	Evidence of heterogeneity
Mother	Female	9	1.50 (1.04-2.14)	Yes, p=0.004
Father	Female	10	1.25 (0.94-1.68)	Yes, p<0.001
Either parent	Female	14	1.11 (0.87-1.42)	Yes, p<0.001
Either parent	Male	5	0.86 (0.62-1.20)	No, p=0.35
Either parent	Both	6	1.14 (0.77-1.70)	Yes, p<0.001

On page 1217 IARC notes the statistically significant increase in risk among women exposed to ETS from the mother in childhood, and the nonsignificant increase in risk among women exposed from the father in childhood. It comments on the significant heterogeneity and concludes that

"the results on exposure during childhood are less clear that those on exposure from the spouse or at the workplace."

My own meta-analyses[36] consider various sources of exposure but combine results for males, females and sexes combined:

Source of exposure	Studies	Pooled relative risk (95% CI)	Evidence of heterogeneity
All household smokers*	29	1.16 (0.98-1.37)	Yes, p<0.001
Mother (specifically)	9	1.12 (0.80-1.57)	Yes, p<0.03
Father (specifically)	11	0.94 (0.72-1.22)	Yes, p<0.001
Parents (specifically)	5	0.62 (0.49-0.79)	No

* All if available, else parents and siblings, else parents, else mother, else father, i.e. index with maximum apparent exposure.

It can be seen that my analyses show much less indication of an association, and even find a significant negative relationship where the exposure index is specifically both parents. As noted in section 4.4, there are a number of differences between IARC and myself in the data included. One of the reasons IARC gets higher answers is because it incorporates data from Asian studies which apparently only asked about exposure from the parents in adulthood, not childhood, eg. by Shimizu.[9] Another is that, for some unaccountable reason, Table 2.6 omits results from the Boffetta study by sex of the subject relating to exposure from the mother and from the father presented on pages 77 and 79 of the Technical Report.[10] Thus one could replace the relevant NR = not reported results in Table 2.6 by the following:

	Source of exposure	
Sex of subject	Mother	Father
Male	1.31 (0.61-2.79)	0.70 (0.47-1.03)
Female	0.76 (0.46-1.26)	0.69 (0.54-0.87)

These relative risks, one of which is significantly below 1, would have a major effect on their estimates, particularly for female subjects. For example, for female subjects and exposure by the mother, where IARC cites a meta-analysis estimate of 1.50 (1.04-2.14), the results from their own multicentre study, of 0.76 (0.46-1.26), are very much lower.

Though IARC's bottom line conclusion for childhood exposure (that the results are "less clear" than for spousal or workplace exposure) is certainly correct, it is apparent that IARC's meta-analyses are in error, resulting in an overestimate of the true association.

4.12 The no-threshold argument

Although not discussed in section 2.1 at all, section 5.2 of the summary argues that, as active smoking causes lung cancer and as ETS involves exposure to the same carcinogens and toxic substances present in tobacco smoke "there will be some risk of lung cancer" from ETS exposure.

The no-threshold argument that some exposure 'implies' some risk is open to question. Some relevant points should be noted:

1. The mechanism by which tobacco-associated cancer arises is unknown, and there is a wide body of opinion supportive of the view that a threshold is likely to exist for cancer arising by a non-genotoxic mechanism.

2. Even where a genotoxic mechanism pertains, absence of a threshold cannot be inferred with any confidence. In a survey of toxicologists reported in 1992,[74] 28% strongly disagreed and a further 47% disagreed with the statement "There is no safe level of exposure to cancer-causing agents."

3. While nonsmokers may vary in the extent to which they are exposed to ETS and in their susceptibility to the effects of smoke constituents, so that an absence of risk can certainly not be assumed, it is interesting to note that it was not until after evidence of a possible lung cancer risk from ETS first appeared in 1981[75,76] that the argument 'some exposure, therefore risk' started to be used. Although the large 1979 US Surgeon General's Report[77] did not even mention the possibility that ETS might cause lung

cancer, it concluded that smoking did, and exposure to smoke constituents from ETS is evidently not zero.

4.13 Consistency of the results for active smoking and ETS

Although not discussed in section 2.1 at all, the summary claims that the magnitude of the observed risks for ETS is "reasonably consistent with predictions based on studies of active smoking in many populations."

Using an estimate of 20 for the risk of lung cancer in men who currently smoke relative to that in never smokers, an estimate of 1% for the exposure to tobacco smoke of ETS-exposed nonsmokers relative to that of current smokers and assuming a linear no-threshold model, Hackshaw, Law and Wald[1] estimated that the risk of lung cancer in ETS-exposed nonsmokers, relative to that in nonsmokers not exposed to ETS, is 1.19. This indirectly estimated 19% increase was regarded as similar to the estimates of 24% (unadjusted) and 26% (adjusted for bias and confounding) for the increase in lung cancer risk associated with living with a smoker that they derived directly from epidemiological studies of nonsmokers.

The IARC summary may have based their statement on this analysis. In fact, as discussed in detail elsewhere,[6] the estimate of a 19% increase derived by Hackshaw, Law and Wald[1] is far too high even accepting a no-threshold model. Using alternative, more plausible assumptions than they used, the estimated increase would not be 19%, but 0.5%. Such a relative risk, of 1.005, would be undetectable by epidemiological methods if it did exist.

4.14 Has IARC demonstrated that ETS causes lung cancer in humans?

Though there clearly is a statistically significant association of spousal (and workplace) ETS exposure with risk of lung cancer in nonsmokers, a conclusion of causality depends on whether it remains after controlling for bias

and confounding. IARC may have presented updated meta-analyses, but these only address the issue of association. It has not carried out any new analyses attempting to adjust for bias and confounding. Instead it mainly relies on the conclusions of Hackshaw *et al*.[1] It does cite one of our series of five papers[2] but completely misrepresents the findings.

For bias due to misclassification of smoking, IARC appears to suggest that our analyses take no account of the fact that misclassified ever smokers are likely to have substantially less lung cancer risk than non-misclassified ever smokers, when of course they do. Furthermore IARC fails to cite any of our misclassification adjusted estimates which, correctly, take into account the much higher misclassification rate in Asian women. For confounding IARC selectively cites estimates of ours which minimize its effects, while ignoring others that show a greater effect. As a result IARC appears to cite our work as supporting the idea that bias and confounding is of little consequence, when the main thrust of our series of papers is that it was important.

In our paper V[6] we concluded that the association of spousal smoking with lung cancer risk in nonsmokers "essentially disappears" if proper adjustment is made for bias and confounding. IARC has presented no arguments whatsoever to argue against this conclusion. As such IARC clearly has not demonstrated that ETS causes lung cancer in humans. Without this demonstration, IARC cannot show that involuntary smoking should be classified as a Group 1 carcinogen.

5. Breast cancer

Section 5.2 of the IARC summary contains the following:

"Breast cancer

The collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent. Although four of the 10 case-control studies found statistically significant increases in risks,[‡] prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never smokers. The lack of a positive dose-response also argues against a causal interpretation of these findings. Finally, the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking."

This conclusion is based on the data presented in section 2.2 (pages 1271-1284) which contains a summary of data from five prospective studies and 10 case-control studies. Included in this section is Table 2.11 which summarizes study details and relative risk estimates for the prospective studies and Table 2.12 which provides similar information for the case-control studies. These occupy six of the 14 pages, the other eight pages being taken up with summaries of the individual studies. There are no meta-analyses and there is no discussion of the overall evidence except that which appears in section 5.2 as shown above.

[‡] The 2002 Summary said "increased risks" rather than "increases in risks"

In the California EPA report[7] there is a statement that

"All four studies on ETS exposure and breast cancer suggest that exposure to ETS is associated with an increased risk of breast cancer. Despite the consistency of the apparent observation, these results cannot be considered conclusive and must be interpreted cautiously for several reasons."

These reasons include the existence of the association only in subgroups, the lack of dose-response and the apparent conflict with the evidence for active smoking. At the time of the California EPA report, results were not available from the two large prospective studies emphasized by IARC as providing no evidence of an association of ETS exposure with breast cancer (the CPS II study[78] and the Nurses' Health Study).[79]

The data and conclusions relating to breast cancer can be compared with those in the recent summary document 'Epidemiological evidence on environmental tobacco smoke and cancers other than the lung'[80] which I prepared for TMA.

For the prospective data, my review includes one additional study[81] reported only as an abstract, but the general conclusion of a lack of association with ETS exposure is the same. I agree with the IARC Working Group that the data from the CPS II and Nurses' Health Study provide good evidence of a lack of relationship.

The data I consider for case-control studies are quite similar to those considered by IARC. IARC appears to have missed data from two studies[82,83] while for one study, conducted in North Carolina, I cite data from a 2002 paper[84] whereas IARC cites data from two earlier papers.[85,86] My review document[80] agrees with IARC that a proportion of the case-control studies do show a

significant association of breast cancer risk with ETS exposure, but that inference of a causal relationship cannot be made for a number of reasons:

(i) the complete lack of association seen in large, well conducted prospective studies,

(ii) the lack of evidence of a dose-response relationship,

(iii) the incongruity of the results for active and passive smoking and

(iv) the major weaknesses of a number of the case-control studies, which are elaborated further in the text in the Monograph describing the individual studies and in my commentaries on the individual studies in my review series.

Overall, I have no real disagreement with the conclusions expressed on breast cancer and ETS in section 5.2. I find it interesting that here IARC seems so ready to dismiss evidence of a statistically significant association from case-control studies, when so much of the epidemiological data on ETS and lung cancer come from case-control studies.

6. Childhood cancer

Section 5.2 of the summary contains the following:

"*Childhood cancer*
Overall, the findings from studies of childhood cancer and exposure to parental smoking are inconsistent and are likely to be affected by bias. There is a suggestion of a modest association between exposure to maternal tobacco smoke during pregnancy and childhood cancer for all cancer sites combined; however, this is in contrast with the null findings for individual sites. Studies on paternal tobacco smoking suggest a small increased risk for lymphomas, but bias and confounding cannot be ruled out."

This is based on section 2.3 "Childhood cancers" (pages 1284-1308) which includes separate subsections on all sites combined, brain and central nervous system, leukaemias and lymphomas, and other childhood cancers. Associated with the first three of the four subsections are Tables 2.13-2.15 summarizing the relevant evidence.

In 1998 Alison Thornton and I reviewed the evidence relating parental smoking to childhood cancer risk.[87] Our conclusions really aligned very well with those reported by IARC. Most meta-analyses we conducted relating maternal smoking in pregnancy or paternal smoking to cancer overall at various sites did not find a significant association and even where one was seen it was weak and subject to bias. Since that time I have not conducted an updated or formal review, though I have considered some relevant individual papers in my review series as they appear. I therefore cannot, at this time, comment in the same depth as for areas which I have recently reviewed in detail, such as lung cancer and other cancers in adults.

The Monograph follows its normal style of presenting a paragraph on each of the studies, in many cases ended by a sentence reflecting the comments of the

Working Group, which often reflect limitations of the study. For the first three subsections, reliance is clearly placed on the meta-analysis conducted by Boffetta and his colleagues in 2000.[88] This is cited in the final paragraph of each of the subsections, and the text in section 5.2 of the summary to a large part reflects the conclusions of that paper.

Although I agree with the general tenor of the conclusions in the Monograph, I was slightly puzzled by its treatment of the large Sorahan studies[89-91] which, based on large case-control studies of childhood cancer deaths in the UK during different time periods (1953-55, 1971-76 and 1977-81), consistently reported a highly significant positive relationship of childhood cancer risk with paternal but not maternal smoking. The note by the Working Group on page 1292 commented on "the very large sample sizes, the consistent findings over time, the adjustment for potential confounders and the assessment of exposure from mothers and fathers with data for trends." All these comments are about strengths of the study, with no reference to any weaknesses. Why, then, does IARC not consider that paternal smoking causes childhood cancer? As usual with the unfortunate style of the IARC Monographs, it is impossible to tell. In my view, the design of the Sorahan studies is open to criticism. There is a strong possibility of selection bias, with the cases studied representing little more than half the available cases, and the procedure for finding controls involving a process where up to six potential controls were selected for each case, with control parents being contacted in turn until one control family agreed to be interviewed. Also, the information on smoking habits related to current smoking and in cases might have been affected by the cancer of the child.

I note that there is a fairly recent study[92] not considered by the Monograph that adds to the evidence of a lack of relationship of parental smoking with childhood brain cancer. This has the strengths of being very large, multicentre and using a standardized questionnaire across the nine centres in seven countries.

7. Other cancers

Section 5.2 of the summary contains the following:

"Other cancer sites

Data are conflicting and sparse for associations between involuntary smoking and cancers of the nasopharynx, nasal cavity, paranasal sinuses, cervix, gastrointestinal tract and cancers at all sites combined. It is unlikely that any effects are produced in passive smokers that are not produced to a greater extent in active smokers or that types of effects that are not seen in active smokers will be seen in passive smokers."

This is based on section 2.4, "Other cancers," which contains five subsections relating to specific categories. It is of interest to compare the material in these subsections with that in the California EPA report[7] and in my 2003 review for TMA[80].

7.1 All cancer sites combined

Remarkably, the monograph cited results from only three studies[93-95], whereas my review[80] considered six additional studies, all but one published by 1990[96-101]. Most of these references were also missed by the California EPA report[7]. It is clear that the data, which lack any evidence from a large prospective study with appropriate adjustment for confounding variables, and include a number of studies of distinctly dubious design, do not allow any firm conclusions to be drawn.

7.2 Cervix cancer

Results from six studies[53,93,94,97,102,103] are cited in the Monograph, with no reference made to three other relevant studies[98,104,105]. The Monograph points out that the data from prospective studies all indicate a lack of a relationship of ETS with cervix cancer and casts doubts on the results of the Slattery study[102], but other weaknesses of the evidence do not come over, including the failure to adjust for HPV infection in any of the studies. Nor is any meta-analysis of the data

presented. While my own meta-analysis did show a significant elevation in risk (relative risk 1.26, 95% CI 1.05-1.52), I do agree with the Monograph that an effect of ETS has not been established. This is consistent with the conclusions of the California EPA report[7], though that report clearly believes the evidence is more indicative of the possibility of a relationship, as judged by the first sentence of its conclusions:

"There is supportive evidence from epidemiological and biochemical studies implicating a role for ETS exposure in the etiology of cervical cancer in nonsmokers."

7.3 Gastrointestinal cancers

Results are only cited for three studies, a study of colorectal cancer[106], which peculiarly reported that ETS exposure was associated with a significant increase in risk in nonsmoking men and a significant decrease in risk in nonsmoking women, a study[107] which reported a significant increase in risk of both colon and rectal cancer associated with ETS exposure, and a study[108] which reported a significant increase in risk of cancer of the gastric cardia, but no increase in risk of distal gastric cancer associated with ETS exposure. The second of these studies[107] was not known to me when I first saw the Monograph, and the Working Group considers it unclear whether the analysis was restricted to never smokers. Having obtained the paper it seems to me very likely that the analysis was not restricted to never smokers, so is not relevant.

It is surprising to me that no reference is made to the well-known Hirayama study[109] which reported no association of ETS with cancer of the oesophagus, stomach, colon, rectum, liver, gall bladder and pancreas, to two other cohort studies[53,97] which each reported no association of ETS with cancer of a number of digestive system cancers, or to another study[110] which reported no association of overall digestive cancer with ETS exposure. These references were all known to the IARC and cited elsewhere. Although the Monograph did not conclude that there is an effect of ETS on gastrointestinal cancers, the data it cited

seem indicative of the possibility that there might be one. Had the Monograph included all the data, the basis for its negative conclusion would have been stronger.

7.4 Nasopharyngeal and nasal sinus cancer

In 1999, the California EPA[7] concluded that nasal sinus cancer was an effect "causally associated with ETS exposure" based on the results of three studies[93,111,112] which "consistently showed a positive association between exposure to ETS and nasal sinus cancer in nonsmokers … with some adjustment for possible confounders." These are the only three published studies of nasal sinus cancer and they are all cited by IARC, who notes the significant associations without offering any criticism of the studies or contributing any discussion about sources of bias. There is no explanation whatsoever as to why the Working Group does not consider that ETS causes nasal sinus cancer.

In my own review[80], I point to a number of limitations of the studies, including the small number of cases studied, the failure in the two Japanese studies[93,111] to control either for the age of the subject or any of the wide range of factors known to be associated with nasal cancer, and the reliance in the US study[112] on data collected from next-of-kin. While I agree with the Working Group that the evidence does not in fact appear conclusive, it would have been nice to know in more detail why it thought so.

The Monograph also refers to two studies of nasopharyngeal cancer (which is quite distinct from nasal sinus cancer), one of which[113] reports a non-significant inverse relationship with ETS exposure, while the other[114] reports significant associations with a number of ETS exposure indices in females but not in males. The Working Group offers no criticism of either study, but does not point out that there are three other relevant studies, two of which[115,116] report no relationship of nasopharyngeal cancer risk with ETS exposure, with the other[117]

reporting a significant association with childhood but not adulthood ETS Exposure. Clearly, the heterogeneous nature of the findings does not allow any clear conclusions and indeed the authors of the study[114] reporting significant associations of nasopharyngeal cancer risk with ETS exposure in females regard their results as "inconclusive as to whether passive smoking contributes to NPC risk."

7.5 Tumours of the brain and central nervous system

The Monograph cites the results of only one study[118]. The results of this study generally show no relationship of brain cancer to ETS exposure, but the Monograph refers to a significant increased risk of meningioma in females associated with ETS exposure (relative risk 2.7, 95% CI 1.2-6.1). However, this analysis is not restricted to nonsmokers, and the analysis that is restricted to nonsmokers in the source paper does not show a significant relationship. Also, the Monograph fails to cite results from five other studies[110,119-122], all of which report no significant association with any index of ETS exposure.

7.6 Other tumour sites

Limited data are available relating to cancer of a number of other sites not considered by IARC, with four studies on bladder cancer and one or two studies on a variety of other sites[80]. The results from these would not alter the general conclusions reached by IARC for 'other cancers' but a more complete coverage of the data would have carried greater conviction.

8. Carcinogenicity of mixtures of mainstream and sidestream tobacco smoke in animals

The evaluation of

"limited evidence in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke"

is based on the first two paragraphs of section 5.3 which state:

"Secondhand tobacco smoke for carcinogenicity studies in animals is produced by machines that simulate human active smoking patterns and combine mainstream and sidestream smoke in various proportions. Such mixtures have been tested for carcinogenicity by inhalation studies in rodents. The experimental model systems for exposure to secondhand tobacco smoke do not fully simulate human exposures, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of secondhand tobacco smoke.

"A mixture of 89% sidestream smoke and 11% mainstream smoke has been tested for carcinogenic activity in mouse strains that are highly susceptible to lung tumours (strains A/J and Swiss). In strain A/J mice, this mixture consistently produces a significant, modest increase in lung tumour incidence and lung tumour multiplicity when the mice are exposed for 5 months followed by a 4-month recovery period. These lung tumours are predominantly adenomas. Continuous exposure of strain A/J mice to the above mixture of mainstream and sidestream tobacco smoke for 9 months with no recovery period did not increase the incidence of lung tumours. In Swiss strain mice, the same mixture induced lung tumours by both protocols, i.e. when the animals were exposed for 5 months followed by a 4-month recovery period and when they were exposed continuously for 9 months with no recovery period. In addition, exposure of Swiss mice to the tobacco smoke mixture for a shorter period was sufficient to induce lung tumours."

This section itself reflects the text in section 3.1 (pages 1323-1329) entitled "Inhalation exposure : simulated environmental tobacco smoke." Looking at the data presented, it is clear that A/J and Swiss mice show an increase in lung tumour incidence following exposure to simulated environmental tobacco smoke. However, section 3.1 makes it clear that:

(i) The exposure system used in many of the studies (a mixture of 89% sidestream and 11% mainstream tobacco smoke), though designed to mimic human exposure, "provides an exposure pattern that differs from that encountered by humans exposed to secondhand smoke."

(ii) The mice used in the studies, whether of the specially inbred strain A/J or the outbred strain Swiss "are highly susceptible to lung tumour development."

(iii) The tumours to which the mice are susceptible "originate primarily from type II pneumocytes, which are precursors for a relatively small fraction (-5-10%) of human adenocarcinomas (ie bronchiolo-alveolar carcinomas)."

(iv) The tumours are predominantly adenomas, which are not cancers.

Though on page 1328 the Monograph notes that tumour incidence is increased when the mice are exposed to "sufficiently high concentrations" of simulated ETS, no comments is made that, in the cited series of studies by Witschi and his colleagues on A/J mice, the exposure to ETS was phenomenally high. Exposure to total suspended particles was typically of over 100 mg/m^3, which is at least 10,000 times higher than median exposures reported in a monitoring study in British nonsmokers.[123]

In reviewing one of the A/J mouse studies[124] my pathologist colleague, Dr F J C Roe, made a number of other points not mentioned by IARC:

(i) ETS exposure was associated with almost a 15% loss in initial body weight, higher than is normally regarded as acceptable in carcinogenesis studies;

(ii) No adjustment has been made for the known effects of calorie intake on lung tumour incidence;[125] and

(iii) The authors claim to have used the diagnostic criteria of Foley *et al*[126] in determining the diagnosis of adenomas, adenocarcinomas and non-proliferative lung lesions. However, their method of assessment of lung tumour incidence appears to be imprecise and unreliable. Firstly, their counts of lung tumours were based solely on the numbers of macroscopically-discernible tumours after fixation in Tellyesniczky's fluid. This method is arguable satisfactory as a rough and ready guide to tumour incidence but, to be really reliable, it needs to be backed up by the microscopic examination of all lesions and also by tumour size data. Such backing-up was not done.

Overall, it is clear that the evidence based on the mouse studies may be totally irrelevant to the risk of lung cancer following ETS exposure in humans. I assume that the limited evidence of carcinogenicity evaluation arises because of the various doubts about the appropriateness of the animal model, rather than any doubts as to whether, if susceptible mice are given a gigantic dose of simulated ETS, an increased incidence of lung tumours (which are mainly benign and atypical of most human lung cancers) arises.

Shorter-term animal inhalation studies with ETS are considered later (see section 11.2 of my comments).

9. Carcinogenicity of condensates of sidestream tobacco smoke to animals

The evaluation that

"there is sufficient evidence in experimental animals for the carcinogenicity of sidestream smoke condensates"

is based on the following part of section 3 in the summary:

"Condensates of sidestream and of mainstream smoke have been tested for carcinogenicity. Both kinds of condensates produced a spectrum of benign and malignant skin tumours in mice following topical application, and the sidestream condensate exhibited higher carcinogenic activity. Sidestream smoke condensate was shown to produce a dose-dependent increase in lung tumours in rats following implantation into the lungs."

This itself is based on section 3.2, "Administration of condensates of sidestream smoke," which is divided into subsections on the mouse and the rat. Both subsections are very short, each dealing with one study.

The single mouse study cited[11] is one in which groups of mice were administered 5, 10 or 15 mg/week mainstream or sidestream smoke condensate for 3 months by skin painting, or were control groups, and were then followed for life. The study and the paper have a number of weaknesses not mentioned by IARC. Thus 39% of the control and 15% of the condensate treated mice could not be examined histopathologically because of the mice fighting, thus causing severe skin injuries, overnight post-mortem autolysis and cannibalism. Regulatory authorities usually regard this as totally unacceptable. Furthermore, dosing was only for a period of 3 months instead of for life, as would be usual when trying to mimic lifetime exposure. Also, the main statistical analyses were inappropriate in that they considered all skin lesions, grouping squamous cell carcinomas and squamous cell papillomas (one a cancer, and one not) with mammary tumours which are histologically quite different. However, even if one

restricts attention to malignant epithelial tumours (arguably most relevant to human lung cancer), the difference between the sidestream condensate treated groups (10 cases in 183 mice) and the mainstream condensate treated groups (0 cases in 177) mice is quite clear, and the results of this study certainly support the general conclusion on page 1329 that "the overall carcinogenicity effect of sidestream smoke condensate was significantly higher than that of mainstream smoke condensate."

It is actually far from surprising that on a weight for weight basis sidestream smoke condensate is more tumorigenic than mainstream smoke condensate, and though the experiment has flaws its main conclusion is clear enough. Really the finding is little more than a reflection of the fact that the concentrations of carcinogens are higher in sidestream smoke and sidestream smoke condensates than in mainstream smoke and mainstream smoke condensates. The problem of course is that humans do not inhale neat sidestream smoke, but instead inhale ETS which is aged, vastly diluted sidestream smoke. A mouse skin study comparing ETS with mainstream smoke condensate would seem far more relevant.

The single rat study cited[12] compares four groups in which different fractions of sidestream smoke condensate were implanted into the lungs. The frequency of lung carcinomas in the four groups (0/35 for semivolatiles, 1/35 for no PAHs or PAHs of 2 and 3 rings, 5/35 for PAHs with four and more rings at a dose of 1.06 mg/rat and 2/5 for PAHs with four or more rings at a dose of 6.4 mg/rat) are given, but it is not made clear how the results allow estimation of the carcinogenicity of sidestream smoke condensate itself.

Are these really the only two studies providing information on the carcinogenicity of sidestream smoke condensate? Are they relevant to human ETS exposure?

10. Effects in household pets

In the summary two references are made to the evidence relating to cancer in household pets. In section 5.3 it is stated that

"Increased relative risks for lung and sinonasal cancer have been reported in companion animals (dogs) exposed to secondhand tobacco smoke in homes."

while in the evaluation section 5.5 it is stated that

"In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs."

This relates back to section 3.3 of the Monograph, "Observational studies of cancer in companion animals," which discusses the results of five studies in which cancer risk in pet animals has been related to their ETS exposure. Four of these studies related to dogs, one to cats.

The only dog study relating to lung cancer[13] was small and showed no significant association of ETS exposure to risk. A reported difference in risk between dogs with long noses and those with short or medium length noses was also not significant. This study is clearly inconclusive.

Two dog studies related to cancer of the nasal cavity and paranasal sinuses. One[14] found no association of risk with presence of smoker in the home when all dogs were considered (odds ratio 1.1, 95% CI 0.7-1.8), but IARC follows the original author in pointing out the increased risk in long nosed dogs (2.0, 1.0-4.1). Why does it not point out the significantly decreased risk in dogs with short or medium noses (0.5, 0.3-0.9)? IARC does not discuss which dog nose size is the better model for man. In any event, the increase in risk in the long nosed dogs is not clearly statistically significant.

The other dog study of sinonasal cancer[15] found risk was non-significantly decreased when smokers were present in the home.

The final study of dogs[16] reported no association of sidestream cigarette smoke to the risk of bladder cancer.

Looking at the results of these four studies it seems quite remarkable that IARC should choose to state that "increased relative risks for lung and sinonasal cancer" have been reported, given that none of the overall risk estimates were significant and that they are not even consistently positive. The overall data for pet dogs is not, in my view, even suggestive of an effect of ETS exposure. It is even more remarkable that this weak evidence gets any mention whatsoever in the evaluation section (5.5).

It is also strange that the summary refers only to the evidence on pet dogs, when the data from the single study on pet cats[17] is much more suggestive of an effect. This did in fact find an increased risk of malignant lymphoma for cats exposed to any household tobacco smoke (odds ratio 2.4, 95% CI 1.2-4.5) and reported evidence of a dose-related trend in relation to various aspects of dose or duration. There are a number of reasons (none pointed out by IARC) why these results are inconclusive, including:

(i) failure to adjust for feline leukaemia virus, a major cause of malignant lymphoma in pet cats,

(ii) reliance on a single control group (cats with non-malignant kidney disease) with a disease for which knowledge of the relationship to ETS exposure is at best extremely limited,

(iii) reliance on data collected up to 8 years after diagnosis, and

(iv) use of dose response analyses all including the totally unexposed group (so that the results are highly correlated with those from the simple unexposed/exposed analysis),

but it is not apparent why IARC emphasizes the dog data and does not mention the cat data.

I note that there is a more recent study on oral squamous cell cancer in pet cats by the same group.[127] This reported a possible association of any household ETS exposure with oral cancer risk with an odds ratio of 2.3 that was not statistically significant (p=0.11). This study, which again relied on controls with non-malignant kidney disease, is also inconclusive.

11. Other issues

11.1 Issues relating to section 5.1 of the summary

Apart from the sections in the summary on human and animal carcinogenicity and on the overall evaluation, there are two other sections, 5.1 Exposure data and 5.4 Other relevant data.

Section 5.1 of the IARC summary is as follows:

"Involuntary (or passive) smoking is exposure to secondhand tobacco smoke, which is a mixture of exhaled mainstream smoke and sidestream smoke released from the smouldering cigarette or other smoking device (cigars, pipes, bidis, etc.)[§] and diluted with ambient air. Involuntary smoking involves inhaling carcinogens, as well as other toxic components, that are present in secondhand tobacco smoke. Secondhand tobacco smoke is sometimes referred to as 'environmental' tobacco smoke. Carcinogens that occur in secondhand tobacco smoke include benzene, 1.3-butadiene, benzo[*a*] pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others.

"Secondhand tobacco smoke consists of a gas phase and a particulate phase; it changes during its dilution and distribution in the environment and upon ageing. The concentrations of respirable particles may be elevated substantially in enclosed spaces containing secondhand tobacco smoke. The composition of tobacco smoke inhaled involuntary is variable quantitatively and depends on the smoking patterns of the smokers who are producing the smoke as well as the composition and design of the cigarettes or other smoking devices. The secondhand tobacco smoke produced by smoking cigarettes has been most intensively studied.

"Secondhand tobacco smoke contains nicotine as well as carcinogens and toxins. Nicotine concentrations in the air in

[§] In the 2002 Summary the bracketed statement was "cigar, pipe, bidi, etc."

homes of smokers and in workplaces where smoking is permitted typically range on average from 2 to 10 μg/m^3."

This derives from section 1 of the Monograph, "Composition, exposure and regulations," on pages 1191-1230. Section 5.1 is fairly straightforward and correct. Reading it I only had a few relatively minor comments:

(i) I am not sure why IARC uses the terms 'involuntary smoking' and 'secondhand tobacco smoke.' In the literature 'ETS' and 'passive smoking' are by far the most commonly used terms.

(ii) The summary provides the reader with no clue as to the relative magnitude of exposure to smoke constituents resulting from ETS exposure and from active smoking.

(iii) I am surprised that the summary provides estimates of nicotine concentration in the air but not of uptake levels of nicotine (or tar).

Looking at section 1, few points struck me, partly because of my lesser familiarity with the literature, particularly in the areas of composition and regulation.

On page 1206 I note that there is a WHO definition of passive smoking – exposure for at least 15 minutes per day on more than 1 day per week. I was unaware of this – I am not sure it is a particularly reasonable definition and wonder whether it has been used much.

On page 1207 IARC correctly takes the view that nicotine in foods does not invalidate cotinine as a marker of ETS exposure.

Later on that page IARC states that "Cotinine can be readily measured in blood, urine and even saliva …" Why the "even"? Saliva cotinine has been widely used for 20 years. Cotinine has also been measured in many other body fluids.[128]

On page 1209 IARC states that relatively few biomarker data are available on a population basis, citing only US data. The annual Health Surveys of England also provide similar data.

11.2 Issues relating to section 5.4 of the summary

Turning now to section 5.4, "Other relevant data," one general point to make is that IARC is really only concerned with cancer, with its evaluations concerning carcinogenicity. It is not always clear how certain parts of section 5.4, eg. relating to cardiovascular effects, actually are relevant to the evaluation. To comment on this it is convenient to go through section 5.4. For each part of it I will first cite it, then refer the reader to the part of the related section 4, "Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms," and then give any comments I have.

"Involuntary smoking has been associated with a number of non-neoplastic diseases and adverse effects in never smokers, including both children and adults."

This is an introduction to the rest of this paragraph, which concerns results considered in section 4.2.1, "Toxic effects: humans," on pages 1358-1366.

"Epidemiological studies have demonstrated that exposure to secondhand tobacco smoke is causally associated with coronary heart disease. From the available meta-analyses, it has been estimated that involuntary smoking increases the risk of an acute coronary heart disease event by 25-35%."

The section on ETS and coronary heart disease on pages 1358-1362 of the data is a reiteration of material in three published meta-analyses.[30,129,130] The section is a one-sided projection of one particular interpretation of the data followed by e.g. Law *et al*[30] and makes no mention of alternative views, such as those I have presented with Francis Roe.[19] As pointed out elsewhere,[18] there are a number of reasons why an apparently increased risk of coronary heart disease

associated with spousal smoking cannot be interpreted as strong support for the claim that ETS exposure actually causes the disease. These include failure to find evidence of an association in the two largest studies;[39,131] failure to consider possible lifestyle confounding factors in many studies; reliance on reported rather than objectively measured ETS exposure (the only two studies[132,133] using cotinine finding no relationship with heart disease); and failure to adjust for misclassification of smoking habits, a likely important source of bias according to results from a recent study.[134]

"Adverse effects of involuntary smoking on the respiratory system have also been detected. In adults, the strongest evidence for a causal relation exists for chronic respiratory symptoms. Some effects on lung function have been detected, but their medical relevance is uncertain."

The evidence on the respiratory system is discussed in section 4.2.1(c) on pages 1364-1366. This starts with a brief section referring to various previous published reviews of the evidence and their conclusions. It is then followed by five further subsections dealing in turn with acute effects of sensory irritation and annoyance, chronic respiratory symptoms, lung function testing, chronic obstructive pulmonary disease and asthma.

It is not apparent from what is presented why the summary considers that, in adults, "the strongest evidence for a causal relation exists for chronic respiratory symptoms." The specific data presented on page 1364 make it clear that though a number of early studies showed no association with ETS exposure, several more recent studies did so. However, the brief section contains no discussion of potential weaknesses of any of the studies, makes no attempt to explain why the results of the later studies are more to be relied upon than those of the earlier studies and gives no indication that data from all relevant studies are considered. No meta-analyses are presented and the conclusion reached is not reported to be reached by any of the other major reviews. Why

does IARC not consider that the strongest evidence relates to acute effects, such as on the eyes, nose, throat or airways?

The statement that some effects on lung function have been detected seems stronger than the statement made on page 1363 that there is "suggestive evidence of a causal relation" based on previous major reviews such as the California EPA report.[7] I note that the Monograph makes no statement about asthma induction, though exacerbation of asthma is also listed under the "suggestive evidence of a causal relation" noted above.

"Data on the hormonal and metabolic effects of involuntary smoking are sparse. However, female involuntary smokers do not appear to weigh less than women who are not exposed to secondhand tobacco smoke, a pattern that contrasts with the findings for active smoking. No consistent association of maternal exposure to secondhand smoke with fertility or fecundity has been identified. There is no clear association of passive smoking with age at menopause."

This relates to evidence discussed in parts of section 4.3.1 on pages 1374-1376. No claims of a relationship with ETS exposure are made and I have no comments to make.

"Maternal cigarette smoking has repeatedly been associated with adverse effects on fetal growth: full-term infants born to women who smoke weigh about 200 g less than those born to non-smokers. A smaller adverse effect has been attributed to maternal passive smoking."

This relates to the material presented on page 1375 under "birth outcomes." The 200 g birth weight decrement associated with maternal smoking is clear enough and apparently mainly due to a direct effect of active smoking. It is certainly true, as IARC states, that a smaller adverse effect (of order 25-50 g) "has been attributed" to maternal passive smoking, eg. by the California

EPA,[7] who include it in their causal effects of ETS. IARC appears not to be taking any committal view here. I agree with this as I regard the evidence of causality to be weak. The major problem is confounding by other causes of low birth weight. In a recent review I conducted[135] I noted that few of the studies which adjusted for a large number (8+) of potential confounding variables found a significant relationship of ETS exposure with birth weight, and then only in isolated analysis for specific endpoints, that some studies reporting associations took account of no potential confounding variables at all, and that some of the studies found that adjustment for potential confounding variables markedly weakened the strength of the reported relationship between ETS and reduced birth weight.

"Cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke. Because of its favourable biological half-life and the sensitivity of techniques for quantifying it, cotinine is currently the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns."

Section 4.1.1, concerning absorption, distribution, metabolism and excretion in humans, includes sections on:

(a) tobacco smoke carcinogen biomarkers (pages 1335-1341), which consider biomarkers of NNK uptake, protein adducts and DNA adducts;

(b) other biomarkers (pages 1341-1343) which considers carbon monoxide, nitric oxide, benzene, carboxyhaemaglobin and thiocyanate; and

(c) nicotine and its metabolites as biomarkers (pages 1343-1347).

The statement quoted above from the summary seems appropriate, though I understand that methods are now developed to quantify the sum of six metabolites of nicotine (including cotinine) which may give a better indication of total uptake of nicotine. I am not particularly familiar with the evidence on biomarkers except for cotinine, where I have published a comprehensive review

paper (not cited by IARC) on its strengths and weaknesses.[128] Looking at the material presented in section 4.1.1, I noted a few points:

(i) On page 1343 IARC states that

> "it has been calculated that even very high consumption of these nicotine-containing products [they are referring to dietary sources of nicotine] would equal at most, about 10% of the amount of nicotine generally taken up by nonsmokers exposed to secondhand tobacco smoke (Jarvis 1994; Repace 1994; Pirkle *et al.*, 1996)"

I actually made essentially this point in the literature much earlier in a paper published in 1987.[136]

(ii) On page 1344 it is stated that "In nonsmokers exposed to secondhand tobacco smoke, cotinine levels are typically 0.6-2% of those detected in smokers," citing six references. As Table 2 of my review paper[128] makes clear it is unusual for studies to find that average cotinine levels in smokers are less than 100 times those in nonsmokers, the ratio commonly being estimated as of order 200 to 300. 0.3-1% would seem more appropriate than the figure IARC cites of 0.6-2%. However there are a number of problems in interpreting the ratio as an index of relative exposure, including sampling error, analytical error at low cotinine levels and the contribution of diet.[128]

(iii) Later on that page IARC refers to cut-off values used "to distinguish occasional smokers from nonsmokers exposed to secondhand smoke." I had not thought that it was possible totally to distinguish the two, and that cut-offs are usually used to detect misclassified smokers. In other words they are upper limits for cotinine from ETS exposure in realistic circumstances. As Table 4 of my review paper[128] makes clear, the cut-off values cited by IARC may be a little too low. For cotinine in

serum a number of studies have used 20 or 25 ng/ml as a cut-off, while for cotinine in urine 100 ng/ml (or a 100 ng/mg creatinine) are commonly used values.

"Several studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules, including haemoglobin adducts of aromatic amines and albumin adducts of polycyclic aromatic hydrocarbons, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood but are lower. Fewer studies have investigated DNA adduct levels in white blood cells of exposed and unexposed non-smokers, and most studies have not shown clear differences."

This relates to evidence mainly presented on pages 1338-1341. It is not an area I have studied in detail, and I have no comment to make.

"In studies of urinary biomarkers, metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNAL], have been found to be consistently elevated in involuntary smokers. Levels of these metabolites are 1-5% as great as those found in smokers. The data demonstrating uptake of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a lung carcinogen in rodents, by non-smokers are supportive of a causal link between exposure to secondhand tobacco smoke and development of lung cancer."

The evidence relating to urine levels of NNAL, a biomarker of NNK uptake, is presented on pages 1335-1338, including Table 4.1. The evidence that it is carcinogenic in rats comes from Monograph 68. Though I cannot usefully discuss whether IARC has appropriately reviewed the evidence here, I do feel the Monograph on involuntary smoking lacks a discussion of the relevance of NNAL and NNK to cancer risk in human smokers. I also understand that there may be some doubt as to whether these compounds really are tobacco specific

(R E Thornton, personal communication). In any event, because one can detect carcinogens in the urine of passive smokers, this does not of itself demonstrate that ETS causes cancer. The dose is relevant. (See section 4.12 of my comments).

"The exposure of experimental animals, primarily rodents, to secondhand tobacco smoke has several biological effects that include (i) increases or decreases in the activity of phase I enzymes involved in carcinogen metabolism; (ii) increased expression of nitric oxide synthase, xanthine oxidase and various protein kinases; (iii) the formation of smoke-related DNA adducts in several tissues; and (iv) the presence of urinary biomarkers of exposure to tobacco smoke."

This relates to evidence presented in section 4.1.2 on pages 1347-1358 on which I cannot usefully comment.

"In adult experimental animals, sidestream tobacco smoke has been found to produce changes that are similar to those observed with exposure of humans to secondhand tobacco smoke. These include inflammatory changes in the airways and accelerated formation of arteriosclerotic plaques. Although the changes are often comparatively minor and require exposure to rather elevated concentrations of sidestream smoke, they support the results of human epidemiological studies. During pre- and postnatal exposure, sidestream smoke produces intrauterine growth retardation, changes the pattern of metabolic enzymes in the developing lung, and gives rise to hyperplasia of the pulmonary neuroendocrine cell population. In addition, it adversely affects pulmonary compliance and airway responsiveness to pharmacological challenges."

This relates to the evidence presented in section 4.2.2 on pages 1366-1374. Although I do not propose to make any detailed comments, it is difficult to see how the fact that rather elevated (unrealistically high?) levels of sidestream

smoke (which is not ETS) produces "comparatively minor" changes lends any particular support to the hypothesis that ETS causes cancer in humans.

"In humans, involuntary smoking is associated with increased concentrations of mutagens in urine. Some studies have shown a correlation of urinary mutagenicity with concentrations of urinary cotinine. Increased levels of sister chromatid exchanges have not been observed in involuntary smokers: however, there is some indication of elevated levels in exposed children. Lung tumours from nonsmokers exposed to tobacco smoke contain *TP53* and *KRAS* mutations which are similar to those found in tumours from smokers. The genotoxicity of sidestream smoke, 'environmental' tobacco smoke, sidestream smoke condensate or a mixture of sidestream and mainstream smoke condensates has been demonstrated in experimental systems *in vitro* and *in vivo*."

This relates to the evidence presented in section 4.4 on pages 1377-1383. It is not an area on which I can usefully comment.

12. Summary of comments

12.1 Major comment

IARC considers that involuntary smoking (ie. ETS) is Carcinogenic to Humans, a Group 1 carcinogen. This conclusion crucially depends on IARC's evaluation that there is sufficient evidence that ETS causes lung cancer in humans, since IARC clearly considers the evidence that ETS causes other cancer in humans to be inconclusive. IARC also considers that there is sufficient evidence of the carcinogenicity of sidestream smoke condensates, but this finding on its own could not lead to ETS being classified as a Group 1 carcinogen. For the evidence that ETS causes lung cancer in humans to be considers sufficient IARC requires that a positive association be observed for which "a causal interpretation is considered to be credible" and for which "chance, bias or confounding" can "be ruled out with reasonable confidence."

The epidemiological data considered by IARC demonstrates that the risk of lung cancer in nonsmokers is associated with both spousal smoking and ETS exposure in the workplace. Since these associations are statistically significant, chance can be ruled out as an explanation with reasonable confidence. Since active smoking is the major risk factor for lung cancer in humans, and active smoking and ETS contain essentially the same smoke constituents (albeit at very different doses), a causal interpretation must be regarded as credible. It follows, therefore, that the conclusion that there is sufficient evidence that ETS causes lung cancer in humans (and hence that ETS is a Group 1 carcinogen) depends crucially on IARC's demonstration that bias and confounding can be ruled out with reasonable confidence.

Although IARC presents its own updated meta-analysis of the evidence relating ETS exposure to lung cancer risk in nonsmokers, these analyses are not adjusted for bias or confounding and merely serve to confirm the existence of an association. Instead, the conclusion that the excess risk "remains after controlling for some potential sources of bias and confounding"

relies heavily on previously published meta-analyses of the evidence on spousal smoking and lung cancer in nonsmokers which have adjusted for bias due to misclassification of active smoking status and, in some cases, also dietary confounding and bias due to exposure to secondhand smoke other than the spouse. The majority of these are old and based on limited data, the only two citations in the last 10 years being those of Hackshaw *et al* in 1997[1] and one[2] of our series of five papers.[2-6]

As our series of five papers makes clear, the analyses of Hackshaw *et al* are open to considerable criticism, and do not support their conclusion, as IARC puts it, that "their overestimation due to misclassification bias and potential confounding seems to be balanced by the underestimation due to exposure to secondhand smoke in the reference group." However, IARC completely fails to address the points raised in our series of five papers, and indeed is guilty of misciting our work to such an extent that it appears to be claiming our findings are consistent with its view that any bias due to misclassification or confounding is small.

Thus, for bias due to misclassification of smoking, IARC appears to suggest that our analyses take no account of the fact that misclassified ever smokers are likely to have substantially less lung cancer risk than non-misclassified ever smokers, when of course they do so. Furthermore IARC fails to cite any of our misclassification adjusted estimates which, correctly take into account the well-documented much higher misclassification rate in Asian women. For confounding IARC selectively cites estimates of ours which minimize the effects of confounding, while ignoring others which show a greater effect. IARC also reiterates a claim made by Hackshaw *et al*[1] that those individual epidemiological studies which had attempted to adjust for confounding had generally shown the effect of adjustment was negligible, a claim discussed and shown to be misleading in our paper II.[4] IARC only cites one of our five papers at all (paper III[2]), and does not mention our paper V[6] which concludes that the

association of spousal smoking with lung cancer risk in nonsmokers "essentially disappears" if proper adjustment is made for bias and confounding. IARC has presented no arguments whatsoever to argue against this conclusion. As such IARC clearly has not demonstrated that ETS causes lung cancer in humans, and therefore has not shown that involuntary smoking should be classified as a Group 1 carcinogen.

12.2 Other comments

A considerable number of other comments are made in the text of this document. Some of the more important ones are listed below.

1. The Summary of the Monograph is, with very minor differences, the same as that released on the IARC website in 2002.
2. The style of the Monograph, while following that of previous Monographs, is open to criticism in not containing a section which explains how the Working Group has reached its evaluations based on the data evaluated. One example of this is for cancer of the nasal sinus, where the same evidence, regarded as demonstrating a causal relationship by the California EPA,[7] is not considered so by IARC, with no real explanation for the difference of opinion. While I would regard the conclusions of the California EPA as premature, in view of various weaknesses in the studies reporting an association of ETS exposure with nasal sinus cancer, IARC does not refer to any such weaknesses and it is not at all clear how the conclusions were reached.
3. In a number of areas where I am familiar with the literature, relevant studies (not published recently) are not cited.
4. Relative risks included in meta-analyses are not always appropriate, particularly for lung cancer associated and childhood ETS exposure.
5. Various sources of bias and confounding which might affect the data relating ETS exposure to lung cancer risk in nonsmokers (and indeed to other associations) are not discussed at all.

6. IARC reiterates the claim of Hackshaw *et al*[1] that significant heterogeneity in the relative risk estimates for spousal smoking and lung cancer in nonsmokers can be explained by the results from one study in China,[8] without realizing that this is not actually true.[6] The fact that studies which do not adjust for age and studies which report dose-response results have substantially higher relative risks is never brought to light.
7. IARC's meta-analyses for childhood exposure are substantial overestimates, due partly to inclusion of results from some Asian studies (eg.[9]) which apparently asked only about exposure from parents in adulthood, and partly to omission of relevant results from IARC's own multicentre case-control study.[10]
8. IARC assumes that as active smoking causes lung cancer and as ETS involves exposure to substances similar to those present in tobacco smoke, some risk of lung cancer from ETS exposure will arise, without addressing alternative views to this no-threshold argument.
9. IARC correctly dismisses claims of an association between ETS and breast cancer, based on the complete lack of association seen in large, well conducted prospective studies.
10. IARC correctly argues that the evidence on ETS and childhood cancer is inconclusive.
11. IARC also correctly concludes that the evidence relating ETS exposure to cancer in adults of sites other than the lung (or breast) is inconclusive, though many of the relevant data are not cited.
12. IARC concludes that there is limited evidence in animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke. It considers data on lung tumour incidence in A/J and Swiss mice, the evaluation of the evidence as limited apparently being due to various doubts expressed about the appropriateness of the model.
13. Evaluation of the evidence in experimental animals for the carcinogenicity of sidestream smoke condensate as sufficient appears to be based only on one unsatisfactory skin painting study in mice,[11] and one rat lung

implantation study involving fractions of sidestream smoke condensate.[12] The relevance of such studies to humans is unclear.

14. In its evaluation section, IARC gives prominence to there being "published reports on possible carcinogenic effects of secondhand smoke in household pet dogs." This is surprising given none of the risk estimates in the four studies cited[13-16] are statistically significant and the findings are not even consistently positive. The only companion animal study at all suggestive of a possible effect of ETS is actually in cats,[17] but even this is far from conclusive.

15. The Monograph includes a section on "Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms." Much of this concerns areas, such as genetic effects, on which I cannot usefully comment. It includes a subsection on ETS and coronary heart disease, which fails to make clear severe limitations in the epidemiological and experimental evidence, which I have discussed elsewhere,[18,19] and generally adds nothing new.

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