STATEMENT BY THE COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT TO SCOTH ON ENVIRONMENTAL TOBACCO SMOKE (ETS) AND LUNG CANCER

Introduction

1. We have been asked by the Scientific Committee on Tobacco and Health (SCOTH) to review a submission from the Tobacco Manufacturers Association (TMA) comprising a meta-analysis of epidemiological data and supporting references, and a separate meta-analysis paper prepared by Dr A Hackshaw and Professor N Wald (a member of SCOTH). The data provided by the TMA comprised three volumes of reviews and references originally received by the SCOTH secretariat in 1994, and updated in February 1995. A key part of the TMA submission was a meta-analysis of epidemiological studies prepared by Mr P N Lee which was updated in December 1996. The TMA recently submitted 3 additional supplements dated January 1997 dealing with; misclassification bias, dose response (with and without exposed groups), and use of cotinine as a biomarker for exposure to ETS[*]. We considered all of the submitted information at two meetings in 1997. A further meta-analysis report prepared by an ad-hoc European Working Group was also considered.[1] We have also considered additional published literature on the formation and composition of ETS, the results obtained in animal experiments involving exposure to surrogates of ETS, and information regarding investigations to evaluate the potential genotoxicity and biological interactions of ETS in humans published up to June 1997.

2. Smoking tobacco is the predominant cause of lung cancer with approximately 90% of lung cancer deaths in Western populations attributable to cigarette usage.[2,3,4] A lower percentage of lung cancer deaths may be attributed to tobacco smoking in developing non-Westernised populations.[4] A number of epidemiological assessments undertaken by national regulatory agencies have reported a small but statistically significantly elevated relative risk for lung cancer in passive smokers of between 1.1 to 1.3 ,[3,5,6] whereas other reviewers[7-11] concluded that the observed association is due to uncontrolled confounding and biases in these analyses. However, since many individuals within the population are exposed to ETS, it is important to resolve the scientific issues particularly as only a small increase in risk would be associated with many hundreds of deaths due to lung cancer per year.

3. Regarding the structure of our review, it was agreed to consider firstly the nature and composition of ETS followed by information on exposure and uptake of genotoxic components (eg adduct studies) with particular reference to the lung as the target organ. Finally to critically review the submitted epidemiological meta-analyses. All of the available information has been evaluated in accordance with our guidelines[12] and also with regard to the criteria proposed by Sir Austin Bradford-Hill.[13]

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[*]Some abbreviations used throughout this statement. ETS = Environmental Tobacco Smoke, MS = mainstream smoke, SS = side stream smoke, TSNA = Tobacco Specific Nitrosamine. NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. NNN= N-nitrosonornicotine. NB: Throughout this statement the terms "exposure to ETS" and "passive smoking" have been used interchangeably.

These latter criteria, which are listed below, are generally regarded as being valuable in the consideration as to whether or not an association between an outcome (in this case lung cancer) and a putative risk factor (passive smoking) is causal.[14] A specific reference to each of these criteria in respect of passive smoking and lung cancer has been included in our discussion.

Bradford-Hill criteria

Strength
Consistency
Specificity
Temporality
Biological gradient
Plausibility
Coherence
Experiment
Analogy

Composition of ETS

4. An essential part of our evaluation concerned the chemical composition of ETS and a comparison of this information with data on the composition of mainstream smoke (MS). There is extensive literature on the presence of chemicals in smoke from cigarettes and other tobacco products and many reviews of this information are available.[3,4,15-19] ETS consists predominantly of aged diluted sidestream smoke (SS) and some exhaled MS with each type of smoke comprising both a particulate and vapour phase. MS is derived from direct inhalation of smoke from the mouth end of a cigarette whilst SS is the material released directly into the air from the burning tip of the cigarette plus that which diffuses through the cigarette paper. The physical and chemical characteristics of ETS are dynamic and differ significantly from MS and fresh SS. The size of ETS particles decreases rapidly with time due to evaporation of volatile constituents and thus ETS particles are usually smaller than MS particles (ETS particles are approximately 0.1-0.25 μm MMAD whereas MS are approximately 0.1-0.9 μm MMAD).[3,5,15,17,20] The chemical composition of ETS also changes rapidly with aging and dilution.[21] Nicotine, which is tobacco specific, is present predominantly in the vapour phase of ETS (ca 95%) with a relatively small amount in the particulate phase (ca 5%).[3] Concentrations of ETS particulate nicotine rapidly reduce due to evaporation from particles whilst the concentration of nicotine in vapour may reduce due to adsorption onto surfaces.[3,15]

5. MS has been the subject of extensive investigation and approximately 4,000 chemicals have been identified to date comprising about 95% of the MS weight.[3,4,5] About 10% of these chemicals have been quantified in both MS and SS and these include a lengthy list of known human carcinogens such as 2-naphthylamine, 4-aminobiphenyl, arsenic, hexavalent chromium, vinyl chloride, benzene and a number of genotoxic animal carcinogens that are regarded as potential human carcinogens such as certain polycyclic aromatic hydrocarbons (PAHs, eg benzo(a)pyrene) and nitrosamines (including the Tobacco Specific Nitrosamines (TSNAs) NNK and NNN).[3,4,5,15] Yields per cigarette of some carcinogens have been reported to be greater in SS compared to MS[22-28] as shown in the table below which presents some selected data from the United States National Research Council (NRC)

review.[5] Yields of some individual chemicals and including a number of carcinogens present in SS have been reported to be relatively constant between different commercial brands including filter and non filter brands of cigarettes. [22,24,27]

Phase	Amount MS	Ratio SS/MS
Vapour		
Benzene	12-48 µg	2.5-4.7
N-nitrosodimethylamine	10-40 ng	20-100
N-nitrosodiethylamine	ND-25 ng	<40
N-nitrosopyrrolidine	6-30 ng	6-30
Particulate		
2-Naphthylamine	1.7 ng	30
4-Aminobiphenyl	4.6 ng	31
Benzo(a)anthracene	20-70 ng	2-4
Benzo(a)pyrene	20-40 ng	2.5-3.5
N-nitrosonornicotine	100-3,000 ng	0.5-3
NNK	100-1,000 ng	1-4

6. One research group documented evidence that the use of filters reduced MS emissions from cigarettes but had little effect on SS emission of a number of carcinogens.[22] Thus some reviewers consider that it is misleading to place too much emphasis on MS/SS ratios.[3,15] However we consider it important to note that the data suggest that all three types of smoke MS, SS and ETS contain the same carcinogens and although there will be quantitative differences in composition between different types of smoke, it is likely that the exposure of active and passive smokers to carcinogens will be qualitatively similar. A critical review of the available exposure data on ETS with particular consideration of derived doses of carcinogens in the lung (the target tissue) is given below.

Exposure to carcinogens present in ETS

7. We have considered the available exposure data with particular consideration of the potential exposure of the lung to ETS particles and carcinogens adsorbed to these particles. Several reviews of ETS exposure studies are available.[3,5,15,17] The majority of these studies have involved either static or personal monitoring of exposure to carbon dioxide, nicotine, total or respirable particles or ETS particles (estimated by UV or florescence light techniques, or as solanesol particulate material; solanesol is a tobacco leaf constituent).[3,5,15] There are a number of recent examples of both static monitoring studies[29-33] and personal monitoring studies.[34-36] Fewer investigations have reported data on actual exposures to carcinogens present in ETS in field studies (ie under prevailing ambient conditions without manipulating either smoking or environmental conditions).[3,5,37] However, there are data to show increased concentrations of carcinogens in indoor air either during or following

smoking in respect of benzene, polycyclic aromatic hydrocarbons and nitrosamines thus providing some data on exposure to carcinogens from ETS in field studies.[37-41] Some reviewers have commented on the poor control for extraneous non tobacco related sources of carcinogens in the available field studies of indoor air.[15,37] Many of the carcinogens which can be found in indoor air such as benzene, polycyclic aromatic hydrocarbons and some volatile nitrosamines can be derived from several sources other than ETS.[15,43,44] Exposure to these chemicals will vary depending on location (ie at home, work, or at public venues, during transportation or resulting from leisure activities), local environmental conditions such as cooking of foods and ventilation, and air pollution. A limited number of exposure studies have reported increased concentrations of TSNAs in ETS,[15] or in SS.[45] One report has documented increased air concentrations of TSNAs (NNK and NNN) derived from ETS in a variety of situations including restaurants, bars and trains.[40]

8. Quantifying exposure to the carcinogens in ETS and in particular dose levels in the lung is complicated particularly as the chemical composition of ETS rapidly changes depending on factors controlling the levels of MS and SS such as the number of smokers present, the building or room occupation density, size of building/room, number of cigarette or other tobacco products smoked over a given period, individual smoking patterns (puff rate, inhalation volume and duration) and factors controlling losses such as degradation/modification of vapour and particulate ETS constituents through chemical reaction or UV light, and the dilution of ETS constituents due to ventilation, mixing of components (ie homogeneity of ETS) and/or absorption and desorption from surfaces in the room.[3,5,15,17,46-48] To illustrate the high potential for variation in air levels of ETS, the United States National Research Council (NRC) modeled air levels of respirable particles (RSPs, <2.5 μm) for a range of conditions expected to be encountered in private residences with one smoker consuming 1-2 cigarettes per hour and found RSP levels varied by two orders of magnitude from approximately 17-5,000 $\mu g/m^3$.[5]

9. A large number of the carcinogens associated with ETS are present in the particulate phase. The fraction of ETS particles deposited in the respiratory tract during passive smoking was reported to be $11 \pm 4\%$, ie lower than the fraction of MS particles deposited in the respiratory tract of active smokers ($47\% \pm 13\%$).[49,50] Data from the ICRP66 Lung model reported in the Department of Health Committee on Medical Effects of Air Pollutants report on non-biological particles and health suggest that approximately 42% of 0.05 μm particles and 29% of 0.2 μm particles are deposited in the respiratory tract with a significant proportion of these particles reaching the alveoli.[51] These data suggest that ETS particles (ca 0.1-0.25 μm) will penetrate to all regions of the respiratory tract. One group of investigators has calculated that a higher deposition of ETS particles compared to MS particles will occur in the terminal bronchioles and alveoli of the lung.[52] The respiratory epithelium of the human lung contains cells with appropriate metabolising capacity to activate carcinogens associated with ETS particles (for example polycyclic aromatic hydrocarbons,[53] and tobacco specific nitrosamines such as NNK[54]).

10. Overall we consider that there are sufficient data to conclude that passive smoking results in an increased dose of genotoxic carcinogens to the respiratory tract including the alveolar region of the lung. In the following section we review the available studies which have investigated the biological properties of ETS particles.

Biological properties of ETS

11. ETS particles contain adsorbed genotoxic carcinogens. The following section presents a review of the biological properties of ETS particles and in particular an assessment of the mutagenic potential of urine samples obtained under field conditions and an evaluation of studies in animals and individuals exposed to ETS. In considering the available studies of the biological properties of ETS, we have paid particular attention to information which is important in assessing whether passive smoking results in exposure to and activation of genotoxic carcinogens in the lung. We have compared exposure data reported in these investigations with published information from field studies[15] in order to evaluate degree of exposure to ETS, although we note that only a limited assessment of exposure is possible.

Mutagenic chemicals adsorbed to particles

12. Several research groups have used air sampling techniques in field studies to collect ETS particles and similar methods to collect SS particles during exposure studies. Solvent extracts made from these particles tested in bacterial mutagenicity tests showed the presence of adsorbed mutagenic chemicals which were active in both the presence and absence of an exogenous metabolising fraction.[39,55-62] It is difficult to compare the results of the field studies in view of differing methods used in these investigations, the results of which depend heavily on the rate of smoking, sampling methods, number of particles collected by filters, solvent extraction methods, the mutagenicity test methods adopted and the possible influence of confounding sources of air particles containing adsorbed mutagenic substances. Although data regarding objective measures of actual exposures to ETS in these studies were incomplete, we conclude that the weight of evidence supports the view that exposure to mutagenic particles present in ETS occurs under a wide range of field conditions and therefore it is likely to occur under all conditions of passive smoking.[39,57,61]

Studies in animals

13. Exposure of mice to very high levels of fresh SS is clastogenic inducing micronuclei in polychromatic erythrocytes and exposure of rats to very high levels of either aged diluted or fresh SS induces DNA adducts in a variety of tissues such as the heart, lung, larynx and bladder.[63-66] It has been established that MS is carcinogenic in hamsters and rabbits exposed by inhalation or following the application of MS condensates to the skin of mice and rabbits or intrapulmonary injection in rats.[4] MS condensates may also act as tumour initiators and promoters in animals.[4] SS is carcinogenic in rats when implanted into the lung[67] or in mice following skin application.[68,69] The results of the skin painting studies in mice have also suggested that on a gravimetric basis the carcinogenic potential of SS condensate exceeds that of MS condensate.[68,69] These data show that whole MS and its condensate and SS condensates are carcinogenic in animals and hence we consider it is likely that ETS will also be carcinogenic to animals. However, we note that there are no appropriate life-time bioassays using ETS available to confirm this. We consider that the recent inhalation study where a carcinogenic response was documented in strain A mice exposed to extremely high levels of SS reinforced with some MS was of very limited value and cannot be used to predict hazards to humans.[70,71] Evidence of reversible hyperplasia and squamous metaplasia in the

nasoturbinates accompanied by active chronic inflammation have been documented in short term inhalation studies of aged diluted SS,[72,73] but the relevance of these findings to the potential carcinogenicity of ETS is unclear.

Studies in humans

14. The biological effects of exposure to ETS have been examined in studies involving the measurement of metabolites of carcinogens and the presence of mutagenic substances in urine from exposed individuals. Other relevant studies have investigated chromosomal aberrations and markers of DNA damage (SCEs) in blood lymphocytes and the detection and quantification of carcinogen adducts with DNA and proteins such as haemoglobin or albumin.[33,45,74-85] It was reported in the previous section of this statement (see paragraphs 7-10) that exposure to ETS occurs by inhalation and ETS particles are deposited throughout the respiratory tract which has the necessary metabolic capability to activate carcinogens present in ETS. We therefore consider that the presence of carcinogens and/or their adducts in blood or urine provides clear evidence of exposure of the lung to the ultimate genotoxic carcinogens.

15. There is evidence of a small increase in the concentration of mutagenic substances in urine samples taken from passive smokers in a number of investigations where small groups of individuals were exposed to high levels of ETS for periods of 5-8 hours.[78,79,83] Only one of these studies included partial control for dietary confounding which has been reported to affect the excretion of mutagens in the urine of active smokers.[86] A further exposure study where a small group of subjects were maintained on controlled diets did not find a significant increase in the excretion of urinary mutagens following exposure to high levels of ETS for 8 hours.[33,82] Limited evidence of increased urinary excretion of mutagenic substances following exposure to ETS has been documented in a small survey of waiters and waitresses[80] and in a small survey of blood donors.[87] No evidence for an increase in chromosome aberrations in peripheral lymphocytes was documented in one study involving waiters exposed to ETS in restaurants[74] or in a number of investigations which considered sister chromatid exchanges in blood lymphocytes[74,79-81,84]

16. Some more recent studies examined carcinogen DNA or protein adducts in passive smokers.[33,75-77,81,85] No increase in ^{32}P-postlabelling of DNA was noted in blood monocytes taken from volunteers exposed to high levels of ETS for 8 hours.[33] However, we considered that sampling of blood monocytes was not the most appropriate technique for monitoring exposure to tobacco smoke carcinogens, even in heavy smokers.[88-91] Protein adducts can serve as surrogates for DNA adducts, particularly at low exposure doses[92-94] and thus most recent attention has therefore been focused on the measurements of protein adducts. A short resume of the main results from three critical studies is presented below.

17. Crawford et al found a statistically significant increase in protein adducts of polycyclic aromatic hydrocarbons using albumin as a marker in children whose mothers smoked compared to children whose mothers did not smoke.[75] We note that elevated plasma cotinine was also found in children whose mothers smoked and consider that this study was adequately performed. MaClure et al measured adducts of 4-aminobiphenyl (4-ABP)and 3-aminobiphenyl (3-ABP) with haemoglobin following hydrolysis to release these aromatic

amines. For 4-ABP adducts there was substantial variability in the results limiting the conclusions that could be drawn. Adducts of 3-ABP were more significantly associated with passive smoking.[76] Hammond et al used the same assay as MaClure et al to examine the levels of 4-ABP haemoglobin adducts in pregnant women. Among non-smokers the levels of 4-ABP adducts increased with exposure to ETS. We have considered the results of this study[77] and the subsequent correspondence relating to it[95-96] and consider that the investigation was adequately conducted and results obtained were valid. It has been demonstrated that 4-ABP exposure in individuals with no history of occupational exposure to this chemical is predominantly derived from tobacco smoking[94] and thus the results obtained by Hammond et al provide good evidence that low level exposure to ETS can result in the absorption of genotoxic carcinogens. In a separate study Hecht et al found increased excretion of urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a specific marker for exposure to the tobacco specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in a small group of 5 individuals exposed to a high level of fresh SS smoke for 3 hours.[45] This study provides good evidence to support the view that passive smoking results in exposure of the respiratory tract to tobacco specific carcinogens.

18. Exposure to ETS over a wide range of exposure levels, including those normally encountered in homes, at work and in public places can lead to the inhalation and delivery of genotoxic carcinogens to all parts of the respiratory tract. Furthermore such compounds will be in contact with cells capable of metabolic activation to produce the proximate carcinogens. These data give rise to concern regarding an increased risk of lung cancer in passive smokers. The available information on passive smokers is consistent with that reported for current cigarette smokers where elevated levels of DNA adducts have been documented in samples of lung tissue.[88,97-102] The COC advice on genotoxic carcinogens is to make the prudent assumption that any exposure may be associated with some increased health detriment.[12] This policy is further supported in this specific instance by the approximately linear dose-response relationship between daily consumption of cigarettes by active smokers and lung cancer risk[14] which we consider is consistent with a lack of a threshold. Thus exposure to ETS may be associated with an increased risk of lung cancer, but it is not possible on the basis of these data to make any estimate of the putative increased risk.

Assessment of submitted meta-analysis reports

19. The epidemiological problems regarding passive smoking are common to the evaluation of the potential association between a low level risk factor and disease. These include the requirement for large numbers of individuals in epidemiological investigations in order for the statistical power of these studies to be acceptable with regard to identifying potential associations, the potential for significant confounding by other risk factors for lung cancer, the possibility of publication bias and misclassification bias, and finally the adequacy of exposure estimation. Some research groups have considered it appropriate to evaluate relative risks of lung cancer in passive smokers by undertaking meta-analyses of the available epidemiological data. We note that the two meta-analyses prepared specifically for SCOTH and reviewed in this statement considered essentially the same studies and that the criteria for inclusion and exclusion were clearly stated. We concur with the specific analyses of publication bias which have concluded this is unlikely to be a factor in passive smoking studies,[103,104] but the potential for dietary confounding, misclassification and measurement

error need to be considered. We also note from the meta-analysis reports that there were geographical variations in the rate of misclassification that need to be considered.

20. We have previously considered the role of meta-analysis in the evaluation of cancer epidemiology at a COC symposium involving invited epidemiologists in February 1994 where participants agreed that meta-analysis was an improvement on conventional reviews, although the statistical analysis alone was not helpful without an associated qualitative review (unpublished report). The overall conclusion of the meeting was that a report of a meta-analysis must include 3 stages - a full narrative review, the statistical analysis (random effects and mixed models considered most useful) and careful interpretation of the results. These conclusions are in accordance with published reviews on the conduct, reporting and evaluation of meta-analysis of epidemiological studies of carcinogenesis.[105] We have looked at the meta-analysis reports submitted to us in accordance with these criteria.

Meta-analysis prepared for TMA by PN Lee.

21. The authors considered 44 studies, (39 case-control, 5 prospective). Three case-control studies were of a nested design. Data on smoking were available for 6 categories; husband (n=42), wife (n=13), workplace (n=16), childhood (n= 18), social (n=6), and total ETS exposure (n=15). There was a total of 5220 female non-smoking lung cancer patients and 388 male non-smoking patients considered. The authors noted that almost 80% of studies had not found a statistically significant effect. Meta-analysis was performed using a fixed effects model and the published RR estimates. A significant association was found in the 42 studies which evaluated lung cancer in non-smoking women living with husbands who smoked RR = 1.19 (95% CI 1.10-1.27) unadjusted and 1.16 (95% CI 1.08-1.24) based on published adjusted results. Additional calculations were performed using a random effects model which gave essentially the same estimates RR = 1.22 (95% CI 1.11-1.36) unadjusted and 1.24 (95% CI 1.11-1.39) for adjusted data. The analyses were not adjusted for misclassification bias because the authors noted that this varied considerably between investigations according to culture and situation in which questions were asked. A follow-up analysis which adjusted for misclassification of ever smokers as non-smokers (2.5% for US, Western or European and 10% for Asian studies) was conducted with data from 39 studies and reported that the overall risk estimate was not significant when a concordance ratio of 3 was assumed (RR = 1.06, 95% CI 0.98-1.14). Evidence for a dose response was reported for 10/39 case-control studies. The authors found significant heterogeneity between studies (including geographical, time of study, size of study, and quality of study). Although no heterogeneity by type of study (prospective versus case-control) was reported, the authors did report heterogeneity by type of control group in the case control studies: investigations with hospital or decedent controls had an RR of 1.33 (95% CI 1.16-1.52) compared to an RR of 1.06 (95% CI 0.96-1.16) for studies with general population controls. The authors proposed that misclassification, uncontrolled confounding, publication bias, recall bias, and inconsistencies between cases and controls could explain the weak association and dose response for lung cancer found in non-smoking women living with men who smoked. The authors also noted that there was no statistically significant association between lung cancer and any other exposure index for ETS (ie exposure during childhood or at work). The authors also concluded that "When all the results are considered, and even when meta-analysis is used, the epidemiological data do not support an inference of causality or even

genuinely elevated risk."

22. We consider that the meta-analysis prepared for the TMA provides a limited narrative review of the studies included, and note that appropriate sensitivity analyses were not undertaken and also that the overall assessment has been based on meta-analyses using the fixed effects model rather than the preferred random effects model. However, we agree that there is little difference between the results obtained in this paper using either model in respect of the data on smoking by the husband. We note that the results obtained for smoking by the husband [unadjusted RR = 1.19 (95% CI 1.10-1.27) and adjusted RR = 1.16 (95% CI 1.08-1.24)] and smoking by the spouse [unadjusted RR = 1.19 (95% CI 1.11-1.28) and adjusted RR = 1.17 (95% CI 1.09-1.25)] were consistent with the meta-analysis conducted by the US Environmental Protection Agency (EPA).[3] There was generally good consistency of the data when all information on spousal smoking was considered and that geographical heterogeneity may have been introduced by one particular paper from China[106] which reported an implausible protective effect of passive smoking, but the appropriate analyses to investigate this possibility were not available. The meta-analysis report identified potential sources of confounding and bias in epidemiological studies of passive smoking but the only adjustment undertaken was for misclassification bias in a supplementary report. We note that no assessment of the dose-response was undertaken in the meta-analysis and consider that the assessment of dose-response by evaluation of the statistical significance of results obtained in individual investigations was not appropriate as many of these studies had limited statistical power. We also note that the authors had not considered under-estimation bias which would attempt to adjust for the exposure of referent groups to ETS.

Meta-analysis prepared for SCOTH by Hackshaw and Wald

23. A meta-analysis of 38 studies was undertaken using a random effects model. The reasons for excluding other studies cited in the paper submitted to SCOTH by the TMA were clearly stated. The authors noted that this meta-analysis included 25 more studies that the previous paper on ETS by the same group which was published in 1986.[107] The authors considered that the assessment of ETS exposure in childhood had not been validated and that none of the available epidemiological studies of childhood exposure reported risk of cancer stratified by whether spouse smoked or not. Regarding exposure to ETS at work, the authors noted this varied considerably between different work environments and had not been well defined and was also difficult to quantify in questionnaires. We concur with the authors decision to base their meta-analysis on spousal studies. An interim analysis based on 34 studies reported an overall risk estimate of 1.24 (95% CI 1.11-1.38).[108] In the submitted meta-analysis there were 5 cohort studies and 33 case-control studies. Odds ratios (ORs) were calculated for 30/33 of the case-control studies, the published odds ratio was used for the remaining 3 case-control studies. The authors commented that the calculated ORs were similar to the adjusted relative risk estimates in the published papers. Age-adjusted relative risk estimates were taken from the cohort studies. The majority of results reported in the meta-analysis document considered the 36 studies which presented data on non-smoking women (91% of cohort). There were 4340 lung cancer cases . Nine studies presented separate data for men (263 cases). The pooled RR from the 36 studies was 1.25 (95% CI 1.13-1.38) and was not significantly altered (ie RR = 1.24) if the data for men and for the two studies reporting men and women combined were included. Further meta-analyses using

dose response data from 16 of the studies provided evidence of a dose-response based on number of cigarettes smoked per day by the spouse and number of years women lived with a spouse who smoked. The findings remained statistically significant after adjustment for misclassification bias using an estimate derived from UK data (7%), underestimation bias (due to some exposure of the reference group to ETS) and dietary confounding.

24. This paper presents a narrative review of the methods used and the inclusion criteria, but not of the individual studies. We agree that the methods of analysis were acceptable, based on the random effects model. The overall relative risk estimate of 1.25 (95% CI 1.13-1.38) was consistent with the result obtained by the EPA.[3] No evidence of heterogeneity was reported when one particular study (discussed in paragraph 22 above) was excluded from the analysis.[106] The results of this meta-analysis were subject to careful interpretation with appropriate meta-analysis of dose-response undertaken, adjustment for misclassification bias by current and former smokers and for potential dietary confounding. A sensitivity analysis was performed which suggested that the risk estimate would remain significant, even if a more extreme misclassification rate was assumed. One aspect of the correction for misclassification of ever smokers as non-smokers is of some concern since the data used to make the correction are from the UK. Whether these data are applicable to other, particularly non-westernised, populations is not known. However, we recognise that the best available information was used to adjust for misclassification bias.

25. The authors commented that the excess risk in non-smoking women living with men who smoked is consistent with the calculated level of cotinine (and nicotine) in these individuals compared to active smokers (ca 1%). Preliminary information from a new analysis based on data provided for the 1994 Health Survey for England suggest that the level of cotinine in adults exposed to spousal ETS is about 0.6-0.7% of the level in active smokers.[109] We consider that cotinine is a useful general indicator of recent exposure to ETS[110-114] but cannot be used to quantify accumulated doses of carcinogens attributable to passive smoking . However the risk analysis in this report based on cotinine was generally supportive of the meta-analysis of the epidemiological data. The authors also stated that the concentrations of major tobacco smoke carcinogens in the blood and urine of passive smokers were higher than in unexposed individuals which is consistent with our evaluation of these data reported in paragraph 17 above.

26. The report also comments that pathological indicators of lung cancer (examples quoted included basal cell hyperplasia and squamous cell metaplasia) were more prevalent in women living with men who smoke compared to unexposed women.[115] Overall we consider that results of this study and the most recent follow up report[116] support the view that lung tissues from non-smoking women living with smoking men were more likely to show morphological abnormalities in the bronchial epithelium and mucus glands than similar tissues from non-smoking women living with non-smoking men.

Ad-hoc European Working Group report

27 We also considered a report from an ad-hoc European Working Group. The meta-analysis was only briefly described, for example, there was no narrative explanation of the methods and the account of the criteria for inclusion of studies and evaluation of results was

limited. An overall RR of 1.16 (95% CI 1.08-1.25) unadjusted and 1.08 (1.00-1.16) adjusted was reported. The authors subdivided the studies according to regional groups as follows: USA, Europe, China, HongKong and Japan, and considered that there were significant differences in the results between the groups. It is unclear whether a formal test of heterogeneity was undertaken. We concluded, on inspection of the data provided, that there was unlikely to be significant heterogeneity, but that among the studies from China there were some which showed no evidence of any effect. This may well be due to confounding risk factors such as indoor air pollution, particular to those studies. The authors reviewed the composition of ETS and presented an analysis of the components of ETS commenting on the likely exposure to genotoxic carcinogens present in ETS. However, the relevant published adduct studies regarding exposure to ETS or fresh SS reviewed in paragraph 17 above were not considered by the ad-hoc European Working Group in their report. Overall the analysis of the epidemiological data was similar to that presented in the report commissioned for the TMA and hence the Committee agreed that this report did not add any new relevant information to the consideration of passive smoking and lung cancer.

Consideration of submitted meta-analysis reports

28. Both the submitted meta-analysis reports (prepared for the TMA and for SCOTH) document similar risk estimates that are consistent with the value reported by the EPA in 1992 of between 1.1-1.3. There were however, considerable differences in interpretation of the results. We consider that the Hackshaw and Wald meta-analysis presents a more thorough consideration of the epidemiological data. In particular this document reports a meta-analysis of dose response data and uses the best available data to adjust for dietary confounding, misclassification bias and under estimation of exposure.

Discussion and Conclusion

29. The consideration as to whether passive smoking is causally related to lung cancer starts from the standpoint that active smoking is recognised as a major cause of lung cancer. There is an approximately linear dose-response between daily consumption of cigarettes by active smokers and lung cancer risk,[4] which we consider is consistent with a lack of a threshold. Moreover active smoking is associated with elevated levels of carcinogen DNA adducts in a number of tissues including the lung and with elevated levels of protein adducts including 4-ABP and TSNA haemoglobin adducts.[88,97-102] We conclude that there are sufficient data available to show that ETS contains known genotoxic carcinogens and that exposure to ETS results in increased doses of genotoxic carcinogens to the lung with increased carcinogen-protein adducts also documented in passive smokers. A tabulated summary of the available evidence regarding passive smoking and lung cancer using the criteria established by Sir Austin Bradford-Hill is given below:

Criterion	**Evidence regarding passive smoking**	**Comments**
Strength	No	Only a weak effect would be predicted from the nature of exposure. Three separate meta-analyses reviewed in this statement produced a

		similar overall relative risk of approximately 1.25.
Consistency	Yes	Most of the published meta-analysis studies and the meta-analyses considered in this report show consistent evidence of a small increase in relative risk. No heterogeneity was reported by Hackshaw and Wald when data from one Chinese study was excluded.
Specificity	Not assessed.	Evidence for tumours at other sites has not been considered in this review.
Temporality	Yes	The results of retrospective studies were consistent with the few prospective studies in the meta-analyses where exposure was assessed prior to diagnosis of lung cancer.
Biological gradient	Yes	Demonstrated in meta-analysis submitted to SCOTH by Hackshaw and Wald.
Plausibility	Yes	Evidence of exposure of the lung to genotoxic carcinogens present in ETS, data from published reports of increased carcinogen-protein adducts in passive smokers and the linear nature of the dose response for lung cancer in active smokers, indicate it is plausible that ETS induces lung cancer.
Coherence	Yes	The available information on passive smoking (epidemiological, biological monitoring studies for exposure using cotinine, and evidence from protein adduct investigations) are coherent.
Experiment	Limited	Possible only in animals. Limited evidence that SS which predominantly forms ETS is carcinogenic in animals. Sufficient evidence that MS is carcinogenic in animals. No adequate study with ETS.
Analogy	Yes	An association between passive smoking and lung cancer is consistent with the known causal association for active smoking and lung cancer.

30. Taking all the supporting data into consideration we conclude that there is evidence to satisfy six of the nine criteria and limited evidence for one of the remaining criteria (experiment) established by Bradford-Hill to assess the causality of an exposure-disease association. We would not anticipate the strength criteria to be fulfilled, given the low level of exposure, and there are no data with which to assess specificity. In fulfilling the other criteria, we conclude that passive smoking in non-smokers exposed over a substantial part of their life is associated with a 10-30% increase in the risk of lung cancer which could account for several hundred lung cancer deaths per annum in the UK.

31. Thus in summary our conclusions regarding passive smoking and lung cancer are;

<u>Composition /Exposure</u>

(i) MS, SS and ETS contain the same carcinogens and although there will be quantitative differences in composition between different types of smoke, it is likely that the exposure of active and passive smokers to carcinogens will be qualitatively similar **(Paragraph 6)**. We consider that there are sufficient data to conclude that passive smoking results in an increased dose of genotoxic carcinogens to the respiratory tract and including the alveolar region of the lung. **(paragraph 10)**

Biological properties

(ii) Exposure to mutagenic particles present in ETS occurs under a wide range of field conditions and is likely to occur under all conditions where passive smoking occurs. **(Paragraph 12)**

(iii) Whole MS and its condensate and SS condensates are carcinogenic in animals which suggests that ETS will also be carcinogenic to animals. However we note that there are no appropriate life-time bioassays using ETS available. **(Paragraph 13)**

(iv) Exposure to ETS over a wide range of exposure levels, including those normally encountered in homes, at work and in public places can lead to the inhalation and delivery of genotoxic carcinogens to all parts of the respiratory tract. Furthermore such compounds will be in contact with cells capable of activation to produce the proximate carcinogens. This gives rise to concern regarding increased carcinogenic risk of lung cancer, although it is not possible to make any quantitative estimate of risk from these particular data. The COC advice on genotoxic carcinogens is to make the prudent assumption that any exposure may be associated with some increased health detriment, in this case a risk of lung cancer. **(Paragraph 18)**

Submitted meta-analysis reports

(v) Both the submitted meta-analysis reports (prepared for TMA and for SCOTH) document similar risk estimates that are consistent with the value reported by the EPA in 1992 of between 1.1-1.3. However there are considerable differences in interpretation of the results. We are of the view that the paper prepared for SCOTH by Hackshaw and Wald presents a more thorough consideration of the epidemiological data. In particular this document reports a meta-analysis of dose response data and uses the best available data to adjust for dietary confounding, misclassification bias and under estimation of exposure. (**Paragraph 28)**

Overall conclusion

(vi) Taking all the supporting data into consideration we conclude that passive smoking in non-smokers exposed over a substantial part of their life is associated with a 10-30% increase in the risk of lung cancer which could account for several hundred lung cancer deaths per annum in the UK. **(Paragraph 30)**

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