IARC views on ETS and health

A review of the recent published literature

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1. IARC views in 1986

In 1986, in their monograph 38 on Tobacco Smoking (1), the International Agency "Cancers related to passive exposure to tobacco smoke." This chapter contained three sections:

(a) Cancer

control studies were reviewed briefly. The authors concluded that "Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke possible risk factors for the various cancers studies. 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 their of risk, on the assumption that the smoking habits of spouses are correlated", and that an underestimation of risk."

(b) Cancers

there had been reports that ETS had been related to cancer at all sites, to nasal sinus the lung, but noted that "these findings were at present difficult to interpret, as many

(c) Childhood

reviewed, IARC concluding that the studies did not "provide clear evidence as to whether or not there is a clear association with parental smoking."

Elsewhereinthemonograph,inthelastparagraph
the
ofthenatureofsidestreamandmainstreamsmoke,ofthematerialsabsorbedduring
'passive
commonly
passivesmokinggivesrisetosomeriskofcancer."Itisalsonotedthat"itisunlikely
thatanyeffectswillbeproducedinpassivesmokersthatarenotproducedtoagreater
extent
inpassivesmokers."

2. Later papers by IARC members

2.1 Papers published between 1986 and 1994

This review concerns papers published subsequently by IARC staff members (2-21). The areas covered by each of the papers are summarized in Table 1. It can be seen that lung cancer has been given particular attention, with other topics receiving much less attention.

2.2 The reputation of IARC

Over the years, publications emanating from IARC have generally acquired a good
in
the
as
Evaluation
the IARC scientific publication series.

One
which IARC built their reputation is that, while the latter were compiled by working groups
staff and it is not at all clear that they are necessarily based on the same degree of expertise. Inasmuch as IARC are a part of WHO, and WHO has taken many steps to discourage
scientific objectivity as would reviews prepared by a panel of independent experts.

The
published by IARC staff members since 1986 put forward valid and scientifically defensible views and more generally to judge the quality of the papers.

This
standards that IARC has adopted or endorsed as an institution in reviewing epidemiologic
should be classified as carcinogenic. The final paper will assess how IARC has

approached substances other than ETS in reaching a conclusion concerning carcinogenicity.

2.3 Structureofthisreport

These comments start by looking at the areas considered in less detail in the IARC adulthood considered work is given (section 6). References (section 7) will be given to the specific IARC paper being considered, but usually not to papers cited within that paper. Appendix A (an any case gives full references to of which were not cited in the IARC papers).

3. Possible effects of ETS exposure in childhood

3.1 Cancer

The only paper providing evidence here is that by Trédaniel et al in 1994 (16). It is concerned with two major endpoints, childhood cancer and cancer in adulthood.

With regard to childhood cancer the authors conclude that "The associations between maternal smoking during pregnancy and childhood cancer have been studied intensively, between by either parent during the child's lifetime, has been little studied. Again no clear associations have been identified." These conclusions accord well with those of an unpublished updated describing the relevant evidence reasonably, making appropriate criticisms of some of the and taking account of the various sorts of bias.

One of the problems of the evidence here is that much of it does not relate directly to ETS exposure, but to smoking in pregnancy. There is no guarantee that mothers and, in the paper "exposure to passive smoking during pregnancy and childhood, and cancer risk: the epidemiological evidence" is somewhat misleading since a fetus is not a passive smoker.

As association has been established, and as it is clear that their review is reasonably thorough and thoughtful, there seems little point in going into detail about the specific statements made about childhood cancer.

Thesectiononcancerinadulthood,relatingtoETSexposureinchildhoodis, however,averydifferentaffair,beingatotallysuperficialandinadequatesummaryof the
studies.
testiscancerandmaternalsmokingduringpregnancy,andnocommentneedbemade.

ThestudybySandleretaliscitedasshowingasignificantlyincreasedriskof cancer of haemopoietic tissue in relation to maternal smoking in childhood and a significantly
(and
smoking
Sandlerstudy.Theseinclude

(i) failuretotakeintoaccountsite-specificconfounders,

(ii) selectingascasescancersurvivorsratherthanincidentcancercases,

(iii) selecting
hardly representative of the population at large, nor are those who agree to cooperatewhencontactedbytelephone,and

(iv) obtaining
questionnaires
as
differed.

Aparticularlyseriousweaknessofthereviewistheconclusionfromtheother three studies (Correa, Wu, Janerich) that "there is some consistency of association between
thereisvastlymoreevidenceonthissubjectthanthiswhich,whentakenasawhole, leadstotheconclusionthatthereisnoassociationatall.Inmy1992(26)bookIcited results from 12 studies (Akiba, Correa, Gao, Garfinkel, Janerich, Kabat, Koo, Pershagen,Sobue,Svensson,WuandWu-Williams)whichprovidedestimatesofthe relationship
(from
significantrelativeriskverycloseto1,of0.98(95%limits,0.86-1.12),anestimate

whichhasremainedessentiallyunchangedwiththeinclusionofnewresultsfromthe Brownson,
alistosomeextentmisleading-thus:

Correa

combined,whenitisnormal(toavoidbias)torestrictattentionspecificallytonever smokers.Correaetalreportedthattherewasnosignificantrelationshipifattentionis sorestricted,thoughtheypresentednorelativeriskestimates.

Wu

nonsmokers,Wuetalgavearelativeriskof0.6(95%limits,0.2-1.7)ifeitherparent smoked,hardlysuggestiveofapositiverelationship.

Janerich study - why do Trédaniel et al cite only the relative risk estimate for 25+ smoker-yearsexposure?Theyconcealthefactthattherewasnoelevationofriskfor 1-24 smoker-years exposure and that, overall, those who were exposed to ETS in childhoodandadolescencedidnothaveasignificantlyincreasedriskoflungcancer comparedtothosewhowereexposed.Theyalsodonotpointoutthat"smoker-years" ofexposureisanindexwhich,byitsveryconstruction,isheavilycorrelatedwiththe numberofpersonsinthehousehold.Thisfactorcouldbeassociatedwithdiseaserisk fornumerousreasons,anditwasaclearerrornothaveadjustedforitinthestatistical analysis.

3.2 Otherendpoints

A

thehealthofchildren.Someofthesemerelyciteconclusionsinintroductorysections inpapersmainlyconcernedwithcancer.Forexample:

(i) in supportiveofpossiblemildeffectsonrespiratoryfunction",

(ii) in 1992 Boffetta and Saracci (9) referred to "acute respiratory illnesses (in particularamongchildren)"asbeingamongthehealtheffects"associatedwith ETSexposure",and

(iii) in acknowledged or

their respiratory function parameters are compromised and the growth of respiratory function is slowed down; and finally that there is a correlation betweenpassivesmokingandchildhoodasthma."

The detail, of hospitalization,chronicrespiratorysymptoms,bronchialhypersensitivity,asthmaand pulmonaryfunctiondevelopment,butwithoutcitationofanystudiesinsupportofthis view.Thereisreferencetosomerelevantfacts,viz.

(i) that duringpregnancy,

(ii) that, ofriskfromETS,and

(iii) that ofclearclinicalrelevance.

However, other risk factors associated with these diseases, some of which are associated with parental in possibility insmokersthannonsmokersandmaybepassedontothechild,amechanismthathas nothing are often reported only in some studies - no attempt is made to come to a careful overviewofthetotalevidence.

The data, presenting tables of results for acute respiratory infections (Table I), chronic respiratory and ventilatory function - longitudinal studies (Table IV). However it is totally superficial, the

is
evidence
potential
infectionfromtheparents,andeffectsofsmokinginpregnancy.

The
valueindeterminingwhetherETSexposurehasaneffectornot.

4. Possibleeffectsinadultsotherthanlungcancer

4.1 Heartdisease

Heart

that

the

associatedtoETSexposure."

Only

and even then only half a page and one table is allocated. The authors state in the summary that "in adults, passive smoking seems to be one of the main risk factors for cardiovascular diseases", and in the conclusion section they cite the estimate of Wells (24) that 32,000 US deaths from heart disease in 1987 are a result of passive smoking (though they note this must be considered with caution). Their conclusions are based mainly on the results of 8 studies comparing mortality due to heart disease among nonsmoking

relative risk estimates and confidence intervals in Table 2 of the paper. Seven of the eight

of

be

other

disease in relation to spousal smoking, they believe a causal association is likely. Furthermore, because the relative risk of 1.3 is quite large compared to that for active smoking, which they estimate at 1.7, they conclude that "a substantial portion of the deaths due to heart disease can be attributed to environmental smoking".

This

is confounding by other risk factors - they note that "the force of this relationship is tempered

(nutrition, high cholesterol levels, blood pressure, etc.)" - but even here they do not attempt to consider relevant evidence relating to confounding. For example, a recent paper by Thornton et al (25) admittedly published after the Trédaniel paper, has made it

factors,andthatthisassociationmaywellcauseimportantconfounding.

Amongerrorsofcommissionandomissionintheirreviewarethefollowing:

(i) Failure in both for details of these weaknesses (26) and for references to all the studies which interestingly Trédaniel etal do not give!).

(ii) Failure to point out that both the Hirayama and Helsing studies have reported inconsistent at short extension to the follow-up period.

(iii) Failure to realise that the results cited from Gillis (1984) had been superseded. In correcting and updating the earlier results.

(iv) Misleadingly stating that a dose-relation had been found in some studies when at best it was only evident in certain subgroups. Thus in the Helsing study, the trend in risk in relation to increasing exposure was noted in the paper to be "negligible" in men - indeed the point estimates (1.00, 1.38 and 1.25 for an exposure score of 0, 1-5 and 6+) decreased with increasing positive exposure. Though 1.27 for the same scores) it was clear that the significance of the trend statistic resulted and In the Humble study the authors note that a trend was only seen among high social status whites and even then it was not quite statistically significant ($0.05<p<0.06$).

(v) Failing to consider the possibility of my place that Secondly, there was a strong and statistically significant tendency for smaller studies

known
byLeVoisandLayard(27),basedonthetwohugeAmericanCancerSociety
studiesCPS-IandCPS-II,andbyLayard(28)basedontheNationalMortality
Followback
As
vastlymorethanalltherestoftheevidenceputtogether,shownorelationship
whatsoever
to
wasastrongpossibility.

Summaryofresultsfromrecentlargestudies
relatingheartdiseasemortalitytospousalsmoking

Reference	Study	Sex	Cases	Relativerisk (95%confidencelimits)
27CPS-I		M	7758	0.97(0.90-1.05)
		F	7133	1.03(0.98-1.08)
	CPS-II	M	1966	0.97(0.87-1.08)
		F	1099	1.00(0.88-1.14)
28	NMFS	M	475	0.97(0.73-1.28)
		F	914	0.99(0.84-1.16)

(vi) Failure
a
lower
These
havesubstantiallymoreETSexposurethandopassivelyexposednonsmokers.
They would only seem to make sense in causal terms, if ETS but not active
smoking,
their ETS exposure). This possibility, which in any case seems highly
implausible,isnotevendiscussedinthepaper.

4.2 Non-neoplasticrespiratorydisease

Whileverybriefmentionofapossibleassociationof ETSwithnon-neoplastic respiratory

are

theresultsofacase-controlstudyconductedinAthens. Fourofthefiveauthorsare based

married

whodeniedeverhavingsmoked,andcontrolswere179ever-marriedneversmoking women of the same age who were friends or relatives at the same hospital. After controlling for age and occupation, a dose-related trend analysis showed positive relationships, both with number of cigarettes smoked daily and with lifelong total consumption,

that

tothecauseofCOLD",arguingthattherelativeriskwastoolargetobeexplainedby smoking

risks were 1.0, 0.9, 2.6 and 1.6 for a husband who was a non-smoker, ex-smoker or smokerofupto1ormorethan1packaday)wasunsurprising,givesthemultitudeof factors that may be involved in the aetiology of COLD. The paper is in fact unimpressiveforanumberofreasons,including:

(i) thesignificanceismarginal,andcouldquiteeasilybeduetochance;

(ii) a

exposureofactiveandpassivesmokerstosmokeconstituents;

(iii) COLD

Greece.Itseemsremarkablethatsomanyneversmokingwomenwith COLD couldactuallybefoundinonehospitalin2years;

(iv) Adjustmentforpotentialconfoundingfactorsisverylimited.If,astheauthors state,themultitudeoffactorsinvolvedintheaetiologyofCOLDcould

a

the

aresoimportant,itwassurelyessentialtotakeaccountoftheminanalysis.

(v) Controlsselectedfromthe

extremely

adequateaccountingforpotentialconfoundingfactors.

(vi) Accordingtomyowncalculations Idonotmakethetrendchisquaredvalues anythinglikeassignificantastheauthorsclaim.

The

evidence

arecitedatall,theauthorarrivingatfivegeneralconclusions:

(i) ETScausesirritationofthemucosaeinthenose,throatandupperairways;

(ii) A

cough,phlegmandwheezeispossible,buttheevidenceisunclear;

(iii) Lungfunctionisclearlyrelatedto ETS,thoughmoresensitivemeasurements suchasflow-volumeloopsusuallyshowsomediminutionofperformance;

(iv) ThereisapossibleassociationbetweenETSandCOLD;and

(v) ETStriggersrespiratorysymptomsinasthmatics.

In discussion, the authors refer to possible biases due to inadequate exposure measurement (sounderestimating a true association) and to inclusion of misclassified smokers

at

great value. I will consider their specific claims when I refer to their final paper (17) which, published in 1994, is a much more detailed review of the evidence.

The

ways. A large number of studies are cited, many key results are presented in tabular form, and there is a reasonably long discussion on bias and confounding factors and criteria for a causal association. While the list of potential sources of bias considered includes a number of the important ones (including misclassification of smokers as nonsmokers, misclassification of ETS exposure and confounding) and the major conclusions

"On

effect

plausible, it remains controversial whether ETS exposure is associated with chronic respiratory symptoms and occurrence of chronic obstructive pulmonary disease, including asthma. Most of the studies that have used the most sensitive indicators of pulmonary function have suggested a negative impact of ETS exposure. However, if really present, the physiological significance of such small changes is unclear, and the relationship to long-term changes in lung function is not established."

are eminently reasonable. There are, however, a number of limitations to the review:

(i) All
out flaws in design and analysis, although for a number of studies these have been pointed out in the literature.

(ii) No
rest
no,
White, showing an absolutely massively strong relationship.

(iii) No
where ETS exposure is self-defined, an association between symptoms and reported exposure may arise, not because exposure causes the symptoms, but because the presence of symptoms may be associated with the likelihood of considering oneself exposed (or heavily exposed).

(iv) The structure of the paper does not always make it clear how conclusions are reached. There is a paragraph for each study describing its results, often also expressed in a table, and later a conclusion, but no attempt is made to do any form of meta-analysis or to make it clear what process was used to reach the overall conclusion from the study summaries.

I
review
the earlier paper stated categorically that (translation from French) "passive exposure
to
the later paper refers to the "conflicting evidence [that] exists on the association in asthmatic patients between ETS exposure and appearance of symptoms and functional

abnormalities(includingchangeinbronchialresponsiveness)".

Iamnotfamiliarwiththefullevidenceonalltheendpointsconsideredinthis review(17)andlackoftimeprecludesadetailedcommentaryontheaccuracyand selectiveness
ETStoCOLD.Heredatafrom6studiesarecited(Simecek,Hirayama,Lee,Sandler, KalandidiandEuler)thoughresultsfromonly5aretabulated.Thereviewnotesthat "fouroutof
ETS
byKalandidietal,theyhaveprovidedlimitedinformationandwerebasedonasmall number
givingtheimpressionofapossibleassociationismisleadingforanumberofreasons:

(i) TheSimecekstudydoesnotprovideanyinformationonCOLDetal.Itisa cross-sectional
havebeenconsideredinthatsectiontothereview.

(ii) No
studies(asdescribedinmybook(26)).

(iii) None

(iv) Virtuallyalltheassociationscitedintherelevanttableofthereviewarenot statistically
limits
thesignificantassociationiswithspousalsmokingof1-20cigarettesadaybut notforspousalsmokingof21+cigarettesaday.InthelatterstudytheCOLD relative
seemshigh,at5.65,itisbasedononly2deathsintheunexposedgroup,and would probably not be statistically significant had an exact rather than an asymptotictestbeenused.

4.3 Cancerotherthanthelung

In1993Trédaniel
have
etc.)"andpointedoutthat"thesehypotheses,whichremaintobeconfirmed,wouldbe

very
and
(9).Neitherpaperactuallydetailedordiscussedtheevidence.

Theonlypaperwhichhasinvestigatedtheevidenceinanydepthisthesecond 1993
nasal
aparagraphforeachstudyand,formosttumours,asummarytableofresults.Then, followingsectionsdiscussingtheroleofchance,biasandconfoundingandthecriteria foracausalassociation,thefollowingoverallconclusionisreached.

"No definite conclusions can be drawn at present from a critical review of the epidemiologicalevidence,butthesuggestionofanassociationispresentforsinonasal cancer,
studies
andthebrain,butthesearedifficulttointerpret."

ThereviewcanbecomparedwithChapter4ofmy1992(26)bookwhichalso reviewed

'Overall,itisclearthattheevidenceonETSasapossibleriskfactorforcanceratsites otherthanthelungisfragmentaryandinconclusive.Fromthedataofarthereisno consistent
relationship."

Comparing my chapter and the IARC review (13) reveals a number of deficiencies
oftheevidenceforcancersofparticularsites.

Publication

thattheAmericanCancerSocietyhavetwohugestudieswithrelevantdatathathave failed

thesitesconsidered,allonehasaresinglereportsofassociationsfromsmallstudies, often
cometoadecision.

Failure

theavailableresultsforallcancertypes,whereasIARC'sreviewhasonlyconsidered specifictypes. SinceassociationswithETSwerenotreportedfortheseothercancer types,theeffectofIARC'somissionistogivetheimpressionthattheproportionof reported
investigatealargenumberofcancersitesmaywellproduce"significant"associations bychance. Thus,Hirayamareportedon18cancersitesotherthanthelung,givinga trendchi-squaredandp-valueforeach. Twoweresignificantatthe95%confidence level,
Thesumofsquaresofthe18chi-squaredvaluesis22.88,againcompletelyconsistent withchancevariation.

ConfoundingTrédaniel
asdiet,education,occupation,socialclass,reproductivefactorsandsexualbehaviour. However,
ofthese potential confounding variables. Nor is any attempt made to consider the relevanceofspecificconfounderswhenassumingtheevidenceforspecificcancers.

Study weaknesses No attempt is made by IARC to bring out weaknesses of specific studies. My book highlights weaknesses of a number of the studies including, in particular,

For example, the first Sandler study used as controls a mixture of friends or acquaintances of patients and people randomly selected by telephone sampling, which produced substantial differences in response rates between cases and controls and an obvious

weaknesses.)

Plausibility of associations not seen for active smoking Trédaniel etal correctly note that "the association between ETS exposure and cancers not related to active smoking is difficult to interpret, and necessarily regarded with caution." While this is certainly correct, they then go on to present an argument to the effect that carcinogens in the vapour

tar of mainstream smoke. However, they fail to make the obvious point that active smokers have markedly more ETS exposure than nonsmokers (partly from their own cigarettes

ETS, and not active smoking, caused some specific cancer an increased risk should be observed in smokers.

Breast cancer Trédaniel etal, but not my chapter, include breast cancer in the list of cancers for which a significant association has been reported. Since the two-fold elevation in the second Sandler study was not statistically significant, the conclusion seems to be based on the cited relative risk

of 20+ cigarettes/day of 1.73 (95% confidence limits 1.12-2.66). In fact, as is clearly stated

age

only

but little can be read into this as the analysis partly resulted from "data-dredging", i.e. carrying out multiple tests with no prior hypothesis. In any case, neither Sandler nor Hirayama took into account any potential confounding factors for breast cancer.

Cervix cancer Trédaniel etal fail to point out the strong possibility that associations

reportedintheSlatterystudywerelikelytorepresentuncontrolledconfoundingfrom
exposure
very
times
sexual
ormorehoursperdayfromacrudevalueof14.84toanadjustedvalueof2.96.Since
thenumberofsexualpartnersofthewomaniscleарlyonlyaninaccuratelymeasured
surrogateofHPVinfection(inter
relevant),theadjustmentwillbeincompleteandleavearesidualconfoundingeffect.
Trédaniel
adjustedrelativeriskcouldbeexplainedbythis.

Colorectalcancer Thediscussion byTrédanielетalofthe results fromthesecond
Sandler
and
withriskinwomenreducedbothinrelationtosmokingandlivingwithasmoker,and
riskinmenincreasedinrelationtosmokingandevenmoreinrelationtolivingwitha
smokeraresopeculiar,especiallywhensetagainstevidencefromotherstudies,asto
makeitverylikelythatthereare majorfaultswiththestudy. TrédanielетaldonOt
criticisethestudy,however.

Totalcancer Whendiscussingresultsfortotalcancer TrédanielетaldonOtmakeit
clear
with ETS is only modestly elevated at best, the Miller study reports a very strong
relationship
beingcollectedonsmokingand
unusual
non-cancercasesthusleadingmoreofthecasestobeclassifiedasETSexposed-it
should
ofotherfindingstotallydiscrepantwiththeliterature,e.g.menandwomenhaveno
differenceinlongevityiftheydonotsmokeandthatsmokersoffiltercigarettеshave
reducedlongevitycomparedwithplaincigarettes.

5. Lungcancer

5.1 Conclusionsreached

This section starts by considering the IARC papers relevant to lung cancer in chronological
time.

The paper by Saracci in 1986 (2) was based on a review of evidence from 6 studies, 6 of the 7 considered by IARC Monograph 38 (1), omitting, for no apparent reason,
Monograph 38 in the paper and made a number of his own:

"(a) the
absence
presence of a 'small' excess risk.

(b) in the light of the other available evidence, external to the studies, the interpretation favourable to the presence of a risk becomes definitely more plausible than the alternative.

(c) under these circumstances further epidemiological studies aiming at a direct estimate
study design and conduct, the play of biases, some of which have been alluded to. Unless this is done, the studies stand a good chance of contributing results of a confusing rather than of a clarifying nature."

The
Riboli did not do more than give a summary table of their results and then cite the conclusions
affected by the additional studies.

The paper by Trédaniel etal in 1989 (5) considered evidence from 14 studies. They
is
there is a 25% increase in the risk of bronchial cancer in a non-smoker married to a smoker

stating
estimate
a
habit misclassification. Although the authors stated that (translation from French) "numerous methodological biases can account for some of the results" and refer to a number of relevant confounding factors in discussion (including confounding and publication bias), their further conclusion that they "cannot explain the whole of the increase
source of potential bias into account.

The paper by Saracci and Riboli in the same year (6) is also based on the same
14
and 95% confidence limits presented for each study in relation to spousal smoking (in all
(95% limits 1.20-1.53) was made. Saracci and Riboli concluded that "the available evidence shows that a causal relationship is most likely to exist though the size of the effect, under different circumstances of exposure,

In 1990 Kalandidi etal (8) published results of a case-control study in Greece. One
in any detail. However, in the introductory section, it is pointed out that "overall the association between passive smoking and lung cancer is highly significant and, for practical purposes, chance can be excluded as a possible explanation. On the basis of biologic plausibility and epidemiologic evidence, causality appears the most likely explanation
The
association
(which we will consider elsewhere), the authors did not attempt to revise their overall conclusions regarding ETS and lung cancer, although there is a statement that "three major reports have concluded that the existing data strongly support a causal relation between passive smoking and lung cancer," citing not only the USNRC and Surgeon-General's report, but interestingly IARC Monograph 38 which did not reach this

conclusionatall!

In 1992 Boffetta and Saracci (9) published a relatively brief review of the evidence
(6),
withoutcitingthestudiesortheirresultsindetail,andthencitearecentmeta-analysis carried
1.57),withoutmakingitclearthiswasonlyadraft. Afterdiscussingmethodological problems,
lung
that
tobiasesonly,isbiologicallyplausibleandisgeneralizable."

The
describes the result of an autopsy study. In the introduction, they note that "the associationbetweenexposuretoenvironmentaltobaccosmokeandlungcancer,first reported in 1981, has been supported by the collective evidence of several epidemiological
ofspecialinterestgroupshavechallengedtheepidemiologicalfindings,involvingthe operation
they merely note that "these results provide support to the body of evidence linking passivesmokingtolungcancer."

Thefirstpaperin1993byTrédaniel<u>etal</u>(12)isageneralreviewofpossible health
refer to the various meta-analyses conducted around 1986 based on the 13 primary studies
by
Norareanypotentialsourcesofbiasdiscussed.Itisstatedinthesummarythat"Itis nowrecognizedthatpassivesmokingisamajorriskfactorforprimarylungcancerin non-smokersexposedtotobaccosmoke."

The second paper by Trédaniel et al in 1993 (13) is mainly a review of the evidence
is
(6), and then refer to 13 new case-control studies, for which they present results in tabular
no
significant association between ETS and lung cancer. The paper contains a section on chance,
seem
to
that "ETS-related lung carcinogenesis can be considered as definitely established."

The paper by Saracci in 1994 (14) is really intended as describing some preliminary
and
"passive smoking gives rise to some risk of cancer", without making it clear these conclusions were not based on the epidemiology. For an up-to-date reference on the evidence, he cites the 1991 paper by Pershagen and Simonato.

The
a table of results from 13 case-control studies published since 1986, a table of meta-analysis results from NRC 1986 to EPA 1992, a very brief discussion of some sources of
the previous papers - "In spite of the methodological criticisms which persist, in our opinion the arguments in favour of the danger of passives moking deserve to be taken into
posed [which was should passives moking be recognized as carcinogenic?]."

The second paper by Trédaniel et al in 1994 (16) concerns possible effects of childhood
have
lung cancer." From the data reviewed, the authors consider that "there is some

consistency of association between ETS exposure in childhood and the risk of lung cancer to adulthood," a claim that I have refuted earlier in section 3.1.

The third paper by Trédaniel on non-neoplastic respiratory diseases. In the introduction, they note that "recent assessments by nonsmokers causes disease, most notably lung cancer."

The the evidence on ETS and lung cancer. They present results for two sets of studies, the first essentially considered by Saracci and Riboli in 1989 (in Tables 1 and 2), and the second essentially the additional studies considered in the tables in two of their recent reviews (13 and 15 - in Tables 4 and 6). After a description of various details of the studies, discussion of various sources of bias, and consideration of Bradford-Hill type criteria for causation, they concluded that "in summary, all the available data seem to fulfil ETS and lung cancer among lifelong non-smokers," and that "the causal association between health impact is still debated."

It because of the strong association between active clearly dose, some risk of lung cancer resulting from ETS exposure in non-smokers.

It is also clear that over the period, their views regarding the strength of the epidemiological did not consider the evidence compelling. By 1989, taking into account the additional evidence believe appear to regard the causal relationship as well-established, though Trédaniel's brief 1994

review
be
tothediscussion;Trédaniel,Boffetta,SaracciandHirsch.

In
conclusionsisexamined.

5.2 Selectioncriteriaforstudiesunstated

As Appendix A a recent summary by me of the available evidence from 38 epidemiological
why
data,
(6)
recentreviews,includingthedetailed1994reviewofTrédanieletal(18). Thereis merely reference to excluding studies because of (unstated) "major methodological limitations"andbecausetheyprovided"verylimitedinformation".

5.3 IndexofETSexposurenotstandardized

In Appendix A I separate out results for various indices of ETS exposure; smoking
wife (Table 7), ETS exposure in the workplace (Table 8), childhood ETS exposure (Table9)and
between exposed and unexposed never smoking subjects, allowing meta-analysis, though
in Appendix A Table 1 are in comparable form to the data used in the various meta-analyses
in
(6). However, as will become more apparent below, the data used in IARC's recent reviews
formatatall.

5.4 Effects of failure to include all appropriate studies and particularly of failure to

standardizetheindexofETSexposureconsidered

Table2summarizestheevidencefromtheearlierstudies,correspondingtothe periodcoveredbytheSaracciandRibolireview(6).Foreachstudytherelativerisks citedbySaracciandRiboliandthosecitedlaterbyTrédanieletal(18),aregivenand compared

arealsoshown.Afewpointsshouldbenotedinthistable:

(i) the
covariates).

(ii) the
orcrudeotherwise.

(iii) theEPAestimatesareforfemalesonlyandarebothcrudeandadjusted,taken from Table 5.5 of this report. EPA also give estimates adjusted for misclassificationbutthesearenotshowninTable2.

(iv) theestimatesforTrédanieletalare,forsomestudies,givenindose-response form, with successive estimates for successively increasing level of positive exposure.Allthedataforfemalesaregiven,butnoneofthedataformales.

Studyofthesereultsshowsfirstlythatthereisvirtuallycompleteagreement regarding

Riboli

report,thoughnotinthesourcepaper,andfortheBufflerstudy,whereTrédanieletal decidedtoleaveitoutbecauseoflimitedinformation,thoughithadbeenincludedby everyoneelse.

It

as

the

generally

and that IARC had, as regards the earlier studies, made an attempt to select out comparabledatafortheappropriatestudies.

Table

Appendix A, by the EPA and by Trédaniel et al (13, 15 18) in their tables. Results are shown

in any case not considered by Trédaniel et al, gave results for males. There is considerable agreement between the data reported in Appendix A and by the EPA, though of course, the EPA report, published in 1992, did not give results for a number of the more recent studies.

There

in the data selected, by Trédaniel et al. It is firstly evident that Trédaniel et al have omitted 5 studies (Butler, Geng, Inoue, Lam 1988 and Liu 1991) for which results are included

of "major methodological limitations" or "very limited information." However, no attempt

of

were

not reject.

While

cancer cases in total out of over 4000 for the total evidence, so that their omission has little effect, the same cannot be said for the relative risks selected by Trédaniel et al. They cited in total relative risks for 15 studies. These can be classified into 5 groups:

Indexusedanddatacitedappropriate	7studies
Appropriateindexusedanddatacited,butdata forincorrectindicesalsocited	1study(Shimizu)
Estimategivenforsexescombined,notfemale	1study(Humble)
Estimategivenforheavyexposure,notoverall exposurebutindexcorrect	2studies(Gao,Liu,1993)
Estimategivenforwrongindex,butoverallexposure	2studies(Svensson,Sobue)
Estimategivenforwrongindexandheavyexposure	2studies(Janerich,Brownson 1992)

It is clearly of vital importance to compare like with like. If one is studying spousal smoking, one should select data for spousal smoking or an index as close to it as available. If one is comparing exposed and unexposed groups, one should select appropriate data and not give relative risks for heavy exposure for some studies for no reason. If one wants to study heavy exposure, one should produce a table of results for heavy exposure.

It is abundantly clear for two major reasons that the data selection of Trédaniel et al has dramatically distorted the evidence. In the first place, if one compares the selected single selected data.

	Appropriate estimates (Appendix A) (Trédaniel et al)	Inappropriate estimates	Number of lung cancers
Goo	1.19	1.70	246
Humble	2.20	2.60	20
Shimizu	1.08	4.00,3.20	90
Svensson	1.26	2.10	34
Janerich	0.75	1.11	188
Sobue	1.13	1.50	144
Brownson	1.00	1.80	431
Liu	1.66	2.90	38

This risk values in order to paint a picture that was closer to their beliefs. The distortion is particularly obvious for some studies. For instance, in the Shimizu study, the source

tablegivesrelativerisksrelatingto8sourcesofexposure.6arecloseto1(range0.8-1.2)withonlythetwocitedfigures(forsmokingbythemotherandbythehusband's father)
for
Trédaniel et al instead select an estimate of 1.80 for heavy exposure to a semi-quantitative
andopentorecallbias.

The other indication of distortion of the evidence comes from the fact that Trédaniel
tendedtoemphasizetheirconclusions. Althoughtheydonotcarryoutformalmeta-analysis of all the data available to them, they make a statement starting "On the assumption
clearlysuggeststheybelievethatthemagnitudeoftheassociationhaschangedlittle. Thisimplicitconclusionistotallyincorrect.Hadtheyconductedmeta-analysisofthe updated
reduced.Asisshowninthemeta-analysespresentedbelow,therecentevidenceshows littleornoevidenceofanassociation.

	Husband'ssmoking-meta-analysisrelativerisks(with95%CR)	
1.	Allstudiescurrentlypublished(n=38)	1.13(1.05-1.22)
1a.	Studiespublishedin1981-88(n=22)	1.36(1.21-1.53)
1b.	Studiespublishedin1989-94(n=16)	1.00(0.90-1.10)
2a.	StudiesconsideredbySaracciandRiboli(n=14)	1.30(1.12-1.51)
2b.	Studiespublishedsincethen(n=24)	1.08(0.99-1.18)
3.	AllstudiesconsideredbyTrédanieletal(n=29)	1.13(1.05-1.23)

Thegreatoverestimationofthemagnitudeoftheassociationby Trédanieletal affects
1.13mightariseasaresultofbiasthanthatarelativeriskof1.30or1.35might.

5.5 Failure

Appendix A makes it clear that there is a statistically significant association between
1.13,
makes
or with childhood ETS exposure (0.97, 0.87-1.07). Nor is there any association with social
spouse.

Because
of
that the association is specifically for spousal smoking is never brought out. Indeed results
all until the Trédaniel et al reviews of 1993 and 1994 (13, 15, 18) and then they are mainly
final review (18) refers to "the growing number of studies [that] have addressed other sources
the husband, at work, and in other situations outside the home". When discussing the findings,
only reference to childhood exposure is in the sentence "Recent studies ... include questions on ETS during childhood, with one recently published paper showing a risk limited
here. As noted in section 3.1 also, inadequate treatment of the data relating childhood ETS
of possible effects of ETS exposure in childhood (16).

5.6 Sources of heterogeneity of spousal smoking relative risks

It
to
find
not (which does not establish heterogeneity anyway as this may occur as a result of sampling variation, especially if some studies are based on few deaths), none of the IARC reviews carry out any formal tests of heterogeneity; not even the Saracci and

Riboli
is
smokingby:

(i) region
China,JapanandHongKong.Significantassociationsareevidentfor Europe, JapanandHongKongbutnotforChinaandUSA.

(ii) time - as noted already, recent studies, conducted since 1988, show no associationatall.

(iii) studysize-largestudiestendtoshowlowerrelativeriskthansmallones.

(iv) diagnostic quality - studies with complete or virtually complete histological confirmationshowhigherrelativeriskthanotherstudies.

(v) studyquality-poorstudies(asdefinedbyonesetofcriteriaatleast)showan association,butbetterstudiesdonot.

TheIARCreviewpaperspayverylittleattentiontosuchsourcesofvariation. TheonlymentionsIcanfindatallarethefollowing:

(i) inthe1994Trédanieletalpaper(18)itisstatedthat"thefactthatsimilarrisk estimates
exposed to different environmental factors, argues in favour of a general association
to
region,asnotedabove.

(ii) in the 1993 Trédaniel et al paper (13), commenting on meta-analysis as a technique, it is noted that "the usefulness of such an approach is at least questionable
methodological deficiencies". However, this seems hardly a reason why one should
producedifferentresultsornot.

One must conclude that the reviews pay totally inadequate attention to the possibility of between-study heterogeneity. Inferences that might be drawn from systematicdifferencesinresultsobtainedunderdifferentcircumstancesarenotaddressed

asthesesystematicdifferencesarenotmadeclear.

5.7 Inadequateattentiontostudyquality

In one pointing the paragraphs made.TheonlyreferencesIcouldfindwere:

(i) to the fact that some studies had only a small proportion of histologically confirmedcases(5,18),andthat

(ii) thepowertodetectsignificantdifferenceswaslimitedbysmallsamplesizein somestudies.

Noristhereanyattemptinanyreviewtocategorizestudiesbystudyquality (apart from excluding certain studies because of major [unstated] methodological limitations)alongthelinesofthe"tierquality"scoresoftheEPA.Thisillustratesthe general uncritical acceptance of data by the IARC in these reviews. In IARC monographsinthepasttherehasbeenthetraditionofpointingoutweaknessesinthe studies ofthe paragraph describing these studies, but this has not been implemented in these reviews.

5.8 WhichhistologicaltypeoflungcancerisassociatedwithETSexposure?

In which ETSexposureisassociatedwith. Inviewofthefactthatlungcancerisnotasingle disease, with consider this question at all. No data are presented comparing relative risks for the differenthistologies.

5.9 TheKalandidistudy

The

describestheresultsofahospitalcase-controlstudyconductedinAthensin1987-89. Successful interviews were conducted with 154 lung cancer cases and with 145 orthopaedic

not only were questions asked about active and passive smoking and various demographic

onairpollutionanddiet.Basedonthedatafor91neversmokingcasesand120never smoking

(95%

of

adjusting

inrelationtohighvslowfruitconsumption.

In

felt

effort

assurance that the results of passive smoking do not reflect bias generated from misclassification

various advantages; "all women were interviewed in person by medically qualified interviewersinthehospitalwards;therewereveryfewrefusals,andmostofthelung cancer

thatselectionbiasandthechoiceofcontrolswerepossibleproblemswiththeirstudy.

Thereare,however,anumberofproblemswiththestudyandpapertowhich attentionshouldbedrawn:

(i) single

notsmoke,

(ii) recallbiaswasnotmentioned.ItispossiblerecallofETSexposuremightbe

greater

forcontrolswithmoreminordiseases.

(iii) cytological confirmation of lung cancer is not actually very reliable. Many

studiesinsiston100%histologicalconfirmation.

(iv) the

estimate of 2.11 for ETS seems implausibly large. However, this is not discussed.

(v) the

that

was

smokersnotmentioned?

(vi) given

found, and given, as is generally found, that ETS exposure is negatively correlated with fruit consumption, one would have expected to see that controlling for fruit consumption would have reduced the magnitude and significance

one

significant.Itisunfortunatethatnotenoughdetailsweregiventoexplainthis. Did in fact women married to smokers eat more fruit? Or did the logistic regression

simultaneously

results?Simpletabulationsofthejointdistributionofhusband'ssmokingand fruit

provided.

5.10 Trichopoulosautopsystudy

In1992Trichopoulosetal(10),twooftheauthorsbeingRiboliandSaracci, describedresultsofanautopsystudy.For206menandwomenwhohaddiedfroma causeotherthanrespiratoryorcancerandforwhom"thepreservationofthebronchial epithelium was satisfactory for pathological examination" interviews concerning the smoking

with

index

smokersandhigher,butnotsignificantlyso,amongformersmokersFurthermore,EPPL values were significantly higher among deceased nonsmoking women married to

smokers
tothebodyofevidencelinkingpassivesmokingtolungcancer,eventhoughtheyare
based
thisassociation".

Theauthorsclaimedthattheir"inspirationandmethodologicapproach...drew
heavily
results differed greatly, and that these differences suggested that their index of lung cancer risk (EPPL) probably had nothing to do with lung cancer at all. Thus Trichopoulosetalfound:

(i) higherEPPLvaluesintheyoungthanintheold,
(ii) higherEPPLvaluesinwomenthaninmen,
(iii) noclearrelationshipofEPPLtooccupationoreducation,
(iv) slightlylowerEPPLvaluesinurbanthaninruraldwellers,
(v) noincreaseinEPPLinex-smokers,and
(vi) no dose-response relationship with current smoking, mean EPPL values in currentsmokersof41+cigs/daybeingvirtuallythesameasinnon-smokers.

It was also striking that whereas Auerbach's studies showed a massive difference in incidence
nosuchdifferenceinthestudyofTrichopoulosetal.Thecontrastisillustratedinthe
table
to
valueinpassivesmokerscanbeinterpretedasindicativethatETSiscarcinogenic?

Source	Index	Smoking habits	% *
Auerbach**	Basal cell hyperplasia with atypical nuclei in at least 30% of cells	Current smokers	
		40+/day	85.1
		20-39/day	72.5
		1-19/day	53.9
		Never smoked	0.45
Trichopoulos	EPPL index	Current smokers	
		41+/day	42.9
		21-40/day	61.4
		1-20/day	58.9
		Never smoked	41.3

*% of maximum score possible for Trichopoulos, % sections positive for Auerbach
**Relationship of smoking to other indices used by Auerbach is similar.

The authors, They failed to explain why their results were so different from Auerbach nor to justify use of EPPL as a valid index of lung cancer risk.

5.11 Biologic plausibility

A number of the IARC papers (2,5,9,11,16,18) address the issue of biologic plausibility by some illustrative quotes:

1. Exposure to ETS and mainstream smoke is qualitatively similar

"Passive exposure to ETS implies exposure to components of the sidestream smoke which are of the same nature as those of the mainstream smoke"(2).

"Combustion chemicals. The sidestream smoke has been documented to contain virtually all the same carcinogenic compounds that have been identified in the mainstream smoke inhaled by smokers"(18).

2. Concentration of toxic chemicals is greater in sidestream than in mainstream smoke, though sidestream is diluted in air

"Some
smoke,
than in the much smaller respiratory air spaces of the smoker where the mainstream smoke flows"(2).

(Translation
carcinogens
suggests
give nequal dose to those of [mainstream]"(5).

"More
of them, six are known to be carcinogenic to humans and about 22-28 are carcinogenic to animals ... In general these chemicals are present at higher concentrations in SS than in MS"(9).

"The
as
these carcinogens are often greater in the sidestream smoke"(11).

"Although the exposures to active smoke and ETS are not identical, the latter appears to include most of the tobacco combustion by-products, especially the carcinogens"(16).

"Since sidestream smoke does not pass through the
100 times the weight of carcinogens of mainstream smoke"(18).

3. In terms of cigarette equivalents, the dose from ETS exposure is not negligible

"According
particulate matter (which includes tar), 11 hours of 'severe' exposure to ETS is equivalent to active smoking of one cigarette. This would imply that exposure

to
(orless)perday,uptoperhapsamaximumoftwo"(2).

"Certainstudieshaveestimatedthatthedegreeofexposureofnonsmokersin environmentalsmokingisequivalentto0.1to2cigarettesperday"(12).

4. No
ETSexposure

"No dose-response relating average number of cigarettes smoked per day in regularsmokerstolungcancermortalityratesoffersanindicationofdeparture from
riskinlungcancer"(2).

"The
suggests a log-linear relationship, which implies a small but existent risk for exposuretoverylowlevelsoftobaccosmoke"(9).

"...no threshold has been established for the health risks of tobacco smoke inhalation"(12).

It
tounderstandingtheoverallevidence:

(i) ETSisamixtureofsidestreamandexhaledmainstreamsmokethatisnotonly diluted,butaged.
(ii) Only
haveeveractuallybeendetectedinETS.
(iii) Thefactthattheconcentrationofvariouschemicalsisdifferentinsidestream than
especially misleading of the latest Trédaniel et al paper (18) not to mention dilutionandtosuggestthatsidestreamisinhaleddirectly.
(iv) The fact that the relative concentration of different chemicals varies between sidestream

mainstream may differ. As it is not known what chemicals contribute to the association of lung cancer and active smoking, it is speculative to suggest ETS may be more toxic on a weight-for-weight basis.

(v) Various cigarette-equivalent estimates have been made indicating that in terms of of lung cancer and active smoking, passive smokers on average are exposed to less than the equivalent of 1/100th of a cigarette a day.

(vi) It is impossible, in principle, to prove or disprove the existence a threshold without knowing the mechanisms involved.

(vii) Epidemiological studies of active smoking typically involve lowest exposure groupings which include smokers of 5 or 10 cigarettes a day. There is no evidence excess risk of lung cancer.

While much less strong than IARC's arguments would suggest.

5.12 Studies conducted by IARC

5.12.1 Introduction

As noted in 1987 by Riboli (3) an "ad hoc working group on approaches to the investigation of cancer risk from passive smoking" was held in Lyon in April 1984. "Two broad categories of research were suggested:

(1) Methodological and to ensure that ongoing studies provide answers as unequivocal as possible.

(2) Multicentre epidemiological studies to investigate the smoking and respiratory cancer"

The headings: "Phase 1: methodological investigation" and "Phase 2: an international case-control study on of data from Phase 1 is completed.

Later
tolungcancerbasedonbloodsamplesobtainedfromthecase-controlstudy.

Belowbriefcommentsaremadeonthe3linesofinvestigation.

5.12.2 Methodologicalinvestigations

First results were reported by Riboli et al in 1990 (7). In this study urinary cotinine was determined in a total of 1369 nonsmoking women in 13 centres in 10 countries in North America, Europe and Asia. The Riboli et al paper was really concerned
an
ofmisclassificationofactivesmokingstatusatall(thoughitrejected47womenfrom most
smokers).

Thepaperreported

(i) largeandstatisticallysignificantdifferencebetweenthecentres,
(ii) thatcotinine/creatininelevelsshowedaclearlinearincreasefromthegroupof women
andatwork,
(iii) thatwomenexposedonlyathomehadhigherlevelsthanwomenexposedonly atwork,
(iv) that ETS exposure from the husband was best measured by the number of cigarettes,and
(v) thatETSexposureatworkwasbestmeasuredbydurationofexposure.

A major conclusion was that "when appropriately questioned, nonsmoking womencanprovideareasonablyaccuratedescriptionofETSexposure"andthestudy ledtothedevelopmentofthequestionnaireusedinthemulticentrecase-controlstudy.

Althoughthestudyappearswelldoneanditsmainfindingsareconsistentwith the literature and appear to be valid, the major conclusion is doubtful. It is not emphasised in the paper that since, as they note, cotinine has a short half-life, the

conclusions at best only apply to current ETS exposure. Furthermore, they do not discuss exposure, only whatsoever of cotinine data. Nor is the value of obtaining confirmatory information from other subjects ETS exposure (and smoking habits) is it not worthwhile attempting to obtain data also from other sources than the subject?

Later, in 1995, Riboli etal (20) published a paper entitled "misclassification of smoking This Because high and off lightsmokers" and they concluded that "potential bias due to smoker misclassification is very unlikely to be responsible for the increased health risks observed in epidemiological studies on ETS".

Although cotinine/creatinine or calculations, excess risk anyway. Their paper is misleading also in claiming that the alleged nonsmokers with levels above 150 ng/mg were all lightsmokers, as some of them had quite that their results on level of misclassification are "in agreement with data available previously". This claim was based on comparison with very limited data. If one compares Journal of Smoking-Related Disorders (30)) their misclassification rates are clearly lower

then average. Finally, the claim that bias due to smoking habit misclassification is unimportant
to the EPA and other reports for this conclusion. Another paper of mine, shortly to be published in Statistics of Medicine (31), makes it clear bias is important and that the EPA's
relevant data on misclassification.

Two other papers with IARC members as authors, both published in 1995, concern
on "limitations of biomarkers of exposure in cancer epidemiology". This paper, while quite short, is well argued and makes the point that "there are considerable scientific limitations
current overemphasis on this approach is misplaced, and that biomarkers have both strengths
limitation they refer to is that biomarkers "usually only indicate relatively recent exposures". They also note that "even the best currently available measures of exposure to
questionnaires for the measurement of current exposures, their very short half-life makes them
the
mixtures such as tobacco smoke.

The second 1995 paper, by Riboli et al (21), concerns "validity of urinary biomarkers of exposure to tobacco smoke following prolonged storage". In this study urine samples were collected in 1976/77 from 58 women who had answered questions on
frozen
finding of the study was that "cotinine measurements made in 1988 allowed a clear separation
that concentrations retained their discriminant value even after 10 years of storage". "Validity" refers to "the capacity of an exposure variable to measure the true exposure in

clear
smoking
samplestodeterminereasonablyaccuratelysmokinghabitsasatthetimethesamples was taken, the study would have been strengthened considerably had cotinine determinationsbeencarriedoutatboththtimepoints.

5.12.3 Multicentrelungcancerstudy

Some
(14).Itisnotedthat

(i) "Thestudyisbeingcarriedoutin11centresin7Europeancountries"(14),

(ii) "ETSisthemajorexposurethatistakenintoconsideration"(14),

(iii) "The
exposuresand...diet"(14),

(iv) "It

(v) "Continuouscheckonthevaliditycanbeenvisagedbytakingurinarycotinine measurements..."(6),

(vi) "It will permit, through simultaneous replication in different centres, both an increase
results"(6),

(vii) It
"a power of about 65%, 85% and 95% for detecting with α=0.05 (2-tailed) relative risks of 1.3, 1.4 and 1.5, respectively" (6).

While many aspects of the study seem commendable, it is unlikely that it will avoid all the problems of bias. Thus use of ill cases and healthy controls will lead to problems of recall bias, the cotinine determinations will not allow validation of reported ETS exposure, and there are no corroborative data collected on past smoking habits. Also the sample size may be inadequate, especially if ETS is associated with a relative risk of 1.1 or 1.2, since the later paper (14) talks of conducting the study with only 400 cases and 600 controls. It is interesting to note that Saracci (14) points out that though, for most of the smokers admitted with a provisional diagnosis of lung cancer, the diagnosis is afterwards histologically confirmed, for 50% or more of the nonsmokers it

is not. As a result they have "materially underestimated" the time it will take to accrue enough cases.

No results have yet been reported from this study.

5.12.4 Genetic susceptibility

While genetic susceptibility may well be important in lung cancer, and Saracci's paper (14) describes a few promising leads, the actual study being done is poorly described. It seems that 140 blood samples will be taken from cases and controls in the lung cancer study, but precisely what will be measured in these, and when, remains unclear to me.

5.13 Sources of bias

Many of the papers have sections which deal with the various sources of bias. Misclassification of exposure, misclassification of smoking habits and confounding by other risk factors are dealt with in most of the more detailed reviews (5,6,9,13,15,18), though other sources of bias are considered in some. Some reviews, however, deal with a very limited number of potential biassing factors - notably the 1993 Trédaniel et al (12) which does not mention any. Because the evidence has accumulated over time in some areas and because the latest review (18) mentions all the sources of bias that might theoretically occur, I will restrict attention mainly to discussion of the arguments presented there.

5.13.1 Misclassification of self-reported smoking status

Misclassification of smoking status as a source of bias has been referred to in many of the IARC papers (2,5,6,9,13,15,18), as it was in the IARC Monograph in 1986. The most extensive discussion appears in the last review (18). While that review contains quite a good description of the mechanisms by which bias might occur, the actual discussion of the available evidence, leading to their conclusion that "misclassification of smoking status is not likely to explain the excess risk" is inadequate. It is worth drawing attention to a few points:

(i) They do not carry out their own bias estimations, relying on estimations by the

NRC, Wald and the EPA. As I show in my 1992 book (26) and in more detail in my paper to appear in Statistics of Medicine (31), these estimates are based on unsound methodology.

(ii) They cite very little of the evidence on extent of misclassification. One of the studies they do cite, by Fontham, is almost irrelevant, as cotinine measured from urine samples taken in hospital after diagnosis of lung cancer, is almost irrelevant to the question as to whether the subject was smoking at the time of onset of the disease as many subjects give up smoking around the time they get lung cancer anyway. The other study cited is their own multicentre study (see 5.12.2 above). There is in fact a wide body of evidence (26,30) showing higher misclassification rates than reported in this study.

(iii) They do not make clear to the reader one of the major problems in misclassification adjustment, namely that circumstances of interview strongly affect accuracy of answers made, so that misclassification may be a far more important source of bias for some study designs than others.

(iv) While they correctly point out that ex-smokers are more likely than current smokers to deny smoking and that ex-smokers have a lower risk of lung cancer than current smokers, it does not actually follow that ex-smokers are likely to introduce a smaller bias. It all depends on the relative misclassification rates and the relative risks. In fact, of course, misclassification of ex-smokers has been taken into account in all the major bias estimates.

For a detailed explanation of why misclassification is an important source of bias the reader is referred to my 3 papers demonstrating this:

(a) Accepted by the Journal of Smoking Related Diseases, summarizing evidence from 42 studies on extent of misclassification of current and past smoking (30),

(b) Accepted by the International Archives of Occupational and Environmental Medicine, describing results of a study showing a particularly high misclassification rate in Japanese women (34),

(c) Accepted by Statistics of Medicine, describing in detail how misclassification bias operates, demonstrating errors in methodology used by the EPA to correct for it, describing a sound methodology for bias correction, and showing that, when applied to US or Asian data using appropriate misclassification rates, it can

explain the reported association between spousal smoking and lung cancer in nonsmoking women (31).

Copies of all these papers are available on request.

5.13.2 Misclassification due to responses by surrogates

Trédaniel et al (18) includes a short section entitled "Misclassification of smoking status reported by next-of-kin". In fact the whole of the discussion concerns possible inaccuracy of data on ETS exposure histories reported by next-of-kin, not data on smoking status. These are of course two completely different issues. The discussion of the evidence relating to surrogate response is in fact quite incomplete, and to some extent misleading.

In the first place the impression given that next-of-kin can be used to obtain data of high quality on ETS exposure is surely an overstatement. While in a study of lung cancer in women, the husband may be able to provide reasonably reliable data on his own smoking or that of other smokers in the household, it is difficult to see that he can provide as reliable data on his wife's exposure at childhood, at work, or in adulthood before they were married. Still less will a child be able to know the mother's full history of ETS exposure.

Secondly, Trédaniel et al only refer to the results of one study (by Stockwell) comparing relative risk estimates obtained from subject and surrogate respondents. I am aware of at least 4 others. Thus Garfinkel reporting much higher relative risks for husband smoking where the respondent was a child (RR = 3.19) than if the respondent was the subject (1.00) or the husband (0.92), Humble reported that "when the analyses were performed separately for self- and surrogate-reported cases, the odds ratios were comparably elevated for both groups", Janerich reported lower relative risks for spousal smoking if the respondent was the surrogate (RR=0.44) rather than the subject (RR=0.93), and the 1994 Fontham paper presented data from which one can calculate somewhat higher relative risks for adult ETS exposure for direct rather than surrogate respondents.

Thirdly, Trédaniel et al might have made it clear that there are 7 studies where there is a very marked difference between the proportion of surrogates used for cases and controls. As shown in the table below, all show higher use of surrogates for cases and all are US studies. All these studies would fail the simple study design criterion of comparing like with like.

	% surrogate respondents	
Study	Cases	Controls
Correa 1983	24	11
Garfinkel 1984	88	Not stated, presumed less
Brownson 1987	69	39
Humble 1987	52	0
Brownson 1992	65	0
Stockwell 1992	67	0
Fontham 1994	37	0

Trédaniel et al conclude that "from the scarce evidence available, it does not seem that this type of bias can explain the positive results". While none of the above points raised by me demonstrate that bias has necessarily occurred, Trédaniel et al's conclusion, based on an inadequate look at the data, may be premature. Certainly some studies show variations in relative risk by respondent type that are much greater than the magnitude of the overall association of spousal smoking with ETS exposure. Even though the direction of these variations are inconsistent, one cannot be too confident that bias has not occurred from use of surrogate respondents.

5.13.3 Recall bias

The possibility of recall bias is not mentioned in any of the IARC papers until the 1994 paper of Trédaniel et al (18). There, they correctly refer to "the possibility that a nonsmoking woman ... with lung cancer will falsely inflate the ETS exposure from the spouse in an attempt to find a causal explanation for her disease." They state that Fontham "particularly addressed" this point in their study. Though this is true, and though they note that "the pattern of risk was the same, when cases were compared to colon cancer or population controls", they surprisingly do not mention the possibility specifically mentioned by Fontham in the 1991 paper that "nonsmoking lung cancer

cases and nonsmoking colon cancer cases are not similarly motivated to remember exposures to the tobacco smoke of others". In other words, recall bias may arise because lung cancer cases, specifically, are aware of the much publicized association of both smoking and ETS exposure with lung cancer, so that Fontham's study design does not solve the problem of recall bias.

5.13.4 Misdiagnosis of primary lung cancer

Trédaniel et al (18) refer to the fact that histological verification of lung cancer has not been a requirement in some studies. The argument that results were "similar" in the Trichopoulos study, which did not have this requirement, and in the Garfinkel case-control study, which did, and that "most recent results are based only on histologically confirmed cases" is scarcely a deep analysis of the position. It is misleading anyway, partly as Trichopoulos observed a markedly higher relative risk for spousal smoking, of 2.08 (95% limits 1.20-3.59) than did Garfinkel (1.23, 95% limits 0.81-1.87) partly as these are anyway only two studies out of a much larger number, and partly as many recent studies have not insisted on histological confirmation. As can be seen in the table below, based on the data in Appendix A, there is no time trend towards a requirement of histological confirmation.

Publication date	Studies	Histological confirmation required	
		Yes*	No
1981-86	11	5	6
1987-88	11	6	5
1989-91	8	2	6
1992-95	8	4	4

(*In all or virtually all, 97%+, of cases)

Trédaniel et al also correctly refer to the possibility pointed out by Faccini that, in life, it may be difficult to distinguish a primary from a secondary lung tumour. They might also have referred to the extensive evidence of substantial disagreement between lung cancer as diagnosed clinically, on death certificates, and at post-mortem (33). They are correct to point out that misdiagnosis is likely to understate any association of ETS with lung cancer, unless the disease with which it is confused is more strongly associated with ETS than is lung cancer.

5.13.5 Publication bias

Trédaniel et al make no attempt to use the current available data to test for publication bias. Had they done so, they would have found, as shown below, that there is some evidence. The risk estimates are higher in smaller rather than larger studies, consistent with the probability that those studies which are most likely not to publish their findings are small negative studies (see Appendix A, section 3.3).

Trédaniel et al argue that publication bias might be "active in either direction". This is unlikely to be true in the context of ETS, medical journals being unlikely to have any preference for publishing negative rather than positive studies. Woodward and McMichael might have been unable to find any unpublished studies, but this does not mean much. For instance it was obvious that the American Cancer Society, which had published results from their CPS-II study on active smoking in 1989, had data on ETS which had not been published. It should be noted that this study is very large (about 1.2 million men and women) and is the only prospective study that asked direct questions on ETS exposure, rather than relating risk only to smoking by the spouse.

While publication bias may not be the major issue that it certainly has been for heart disease, the discussion by Trédaniel et al is certainly somewhat misleading.

5.13.6 Confounding

The possibility of confounding by other risk factors was not mentioned until the 1992 paper by Boffetta and Saracci (9). They noted that "diet might play a role, that is spouses of smokers eat less protective foods or more high risk foods than spouses of non-smokers." They cited only two pieces of evidence. One was the Kalandidi study which I have addressed already in section 5.9. The other was the study by Le Marchand et al which "estimated that the confounding effect ... would not be great." In fact, Le Marchand et al estimated that failure to adjust for the single dietary factor, beta-carotene, would result in a 10% over-estimate of the ETS/lung cancer relative risk. A bias of 1.10, in the context of an effect now estimated at less than 1.2, can hardly be described as "not great"!!

The same misleading citation of the Le Marchand study was also made in the second 1993 Trédaniel et al paper (13), the first 1993 Trédaniel et al paper (12) not even considering any potential sources of bias at all. This paper also noted that education, occupation and social class "have also to be taken into account."

The first 1994 Trédaniel et al paper (15) considered diet as the only possible confounder, pointing out correctly that "smokers have a diet which is high in fat and poor in fruits and vegetables, which is associated with an increased risk of lung cancer," and that "this could be the case of nonsmokers sharing the dietary habits of smokers with whom they live." However they referred to three studies (Kalandidi, Wu and Dalager) which adjusted for dietary habits and found this had no effect.

The final 1994 Trédaniel et al paper (18) contains a longer section on confounding. This correctly makes a number of points clear:

(i) "very few data are available on the possible confounding effect of risk factors for

lung cancer other than ETS";

(ii) "diet may be an important confounder";

(iii) "only three [studies] have attempted to adjust for diet and suggested no confounding effect";

(iv) "occupation and social class must also be taken into account";

(v) "exposure to indoor air pollution (including radon) might play an important role";

and concludes that "there is no convincing evidence that these potential confounding factors could have affected the results of these studies."

There are, however, a number of unmade points. Firstly, there is growing evidence that ETS exposure is associated with increased exposure to a range of lung cancer risk factors (25). Just as smokers are more exposed than nonsmokers to virtually every risk factor one can name, it is emerging that the same is true when one compares nonsmokers married to (or living with) smokers and nonsmokers married to (or living with) nonsmokers. This suggests that there must be some confounding effect.

Secondly, it is also not perhaps made clear enough that attention to confounding in many of the studies of ETS and lung cancer has been non-existent or very limited. Even where confounders are taken into account, it is usually impossible to tell from the evidence presented what effect adjustment for specific variables has had.

Thirdly, it is not mentioned that many of the ETS/lung cancer studies (12/38) have failed even to adjust for age. Often these studies had matched <u>overall</u> cases and controls on age, but made the unwarranted assumption that the <u>lifelong never smoking</u> cases and controls would be comparable in age.

Fourthly, it is also not mentioned that about two-thirds (21/31) of the studies using smoking by the husband as an index of ETS exposure had failed to restrict analyses to married women. As the exposed group are all, by force, married but the unexposed group contains a mixture of married and unmarried women, there is an inevitable confounding between possible effects of marital status (and its correlates) and of ETS.

5.13.7 Misclassification of ETS exposure

In 1989 Saracci and Riboli (6) referred to

"two sources of bias [that] may act to decrease the observed relative risk among non-smoking women exposed to ETS via smoking spouses. First this group of women is compared with other non-smokers who, however, are not 'pure' subjects unexposed to any ETS, as some of them may indeed be exposed to other unrecorded sources of ETS (e.g. at work or in public places). Second, random misclassification of exposure tends to dilute any existing effect and its relative risk."

Surprisingly these points are not made in some reviews (e.g. 9, 12, 13) and later reviews (15, 18) only refer to the first of these points. Thus Trédaniel et al in 1994 (18) stated that

"Finally, one must stress that because there is widespread exposure to ETS, the upward bias on the relative risk of lung cancer caused by smoker misclassification is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group."

A number of points should be made here.

(i) The paragraph is under the wrong heading, as it concerns misclassification of ETS exposure, not of smoking by the subject.

(ii) It is not made clear in any paper that in the absence of a true effect of ETS exposure, misclassification of spousal smoking will cause no biasing effect, but misclassification of active smoking habits will cause upward bias (assuming it is random and that there is concordance between smoking habits of husband and wife).

(iii) Even if there is an effect of ETS exposure the counterbalancing of the two biases is not equal.

(iv) Later in the paper Trédaniel et al cite the EPA's conclusion that an ETS/lung cancer relative risk of 1.19 for the US studies adjusted for smoker misclassification rises to 1.59 after adjusting for background ETS sources. Not only is, as noted earlier, the EPA's downward correction for smoker

misclassification markedly too small, but their upward correction for background exposure is markedly too large. Trédaniel et al fail to point out that EPA's estimate (via cotinine levels) of the relative total ETS exposure of nonsmokers married to smokers and nonsmokers married to nonsmokers is very much lower than IARC reported in their multicentre study (7). Using their own data, which are in fact more consistent with other studies, would result in a much smaller upward correction.

5.14 Proof of causation

Trédaniel et al (18) contains a section "ETS and lung cancer: proof of causation" which formally goes through Bradford-Hill type criteria. These are discussed below.

5.14.1 Consistency and strength of association

Trédaniel et al admit that any association with smoking by the husband is weak. However they fail to cite various inconsistencies noted above and do not point out the variation in relative risk over time, with no association reported in studies conducted in recent years. Nor do they point out that the overall evidence shows no association with other indices of ETS exposure, such as workplace, childhood or social exposure.

Weak and inconsistent would be a fairer summary of the evidence.

5.14.2 Specificity

The discussion with regard to histological type is obscure and the paper nowhere addresses the key issue as to whether the evidence suggests that ETS is related to squamous cell carcinoma (strongly associated with active smoking) or adenocarcinoma (weakly associated with active smoking) or both. As noted above, the evidence is in fact conflicting, thus weakening the "proof of causation."

In any case, even IARC would not claim either that lung cancer is specifically caused by ETS exposure or that ETS exposure specifically results in lung cancer. While causality may arise in the absence of specificity, it is clear that the association fails the criterion of "specificity".

5.14.3 Coherence

Though there is evidence of some association between husband's smoking and lung cancer in a number of different countries and continents, this of itself is not strong evidence of a cause and effect relationship. Various sources of bias, such as misclassification of smoking habits and confounding, could not be expected to apply widely. In any case, the risk estimates are not similar. There is, as noted above, statistically significant heterogeneity between relative risk estimates for Europe, Asia and the US; and between estimates for Japan, Hong Kong and China.

5.14.4 Dose-response relationship

The evidence presented in Table 6 is neither comprehensive nor systematically examined. Though published data show a tendency for nonsmoking women married to heavy smokers or to smokers of long duration to have an increased relative risk of lung cancer, there are a number of factors not mentioned by Trédaniel et al which limit interpretation. They fail to note strong evidence that studies which provide dose-response data are highly selective, with the overall relative risk estimate for husband's smoking 1.25 (95% CI 1.14-1.37) for the studies that do provide data, and 0.89 (95% CI 0.78-1.03) for those that do not. Nor do they discuss various other sources of bias (recall bias, confounding, misclassification of smoking) that may create an artificial dose-response. (See Appendix A for further discussion of the evidence on dose-response, which also presents data showing that a dose-response relationship is not clearly evident for ETS exposure indices other than spousal smoking.)

5.14.5 Biological plausibility

No attempt is made to compare relative exposure to smoke constituents from ETS and mainstream smoke. The recent study by Phillips et al (35) suggests that, on average, exposure to particulate matter and nicotine from ETS is some thousands of times lower than that from active smoking. It is difficult to see how one can assess plausibility without taking into account the magnitude of exposure in relation to the magnitude of the claimed effect.

The comment "Since sidestream smoke does not pass through the lung filter it

contains up to 100 times the weight of carcinogens of mainstream smoke" is rather odd and irrelevant. Trédaniel et al ignore the fact that, unlike mainstream smoke, sidestream smoke is massively diluted and aged before it is inhaled.

The reference to the autopsy study of Trichopoulos et al is misleading in failing to point out that the index used (epithelial, possibly precancerous lesions) shows no relationship with active smoking, being similar in lifelong never smokers as in smokers of more than 40 cigarettes a day. Why was an index that is not associated with active smoking used in the context of exposure to ETS?

5.14.6 Animal evidence

Trédaniel et al cite the Reif study (36) as finding a weak relationship. This seems misleading as the relative risk observed was not even close to being statistically significant. They do not refer to the short-term (up to 90 day) ETS inhalation studies that have been done, which show no meaningful changes despite exposure to levels of ETS constituents being much higher than those typically encountered.

5.14.7 Analogy

Trédaniel et al do not make it clear that linear extrapolation from active smoking data would indicate a much lower risk resulting from ETS exposure than might be suggested by the relative risk of 1.13 for smoking by the husband. They also incorrectly cite the dose-response relationship fitted by Doll and Peto. This is quadratic and not log-linear as claimed. Had they used the former the discrepancy in risk would have increased further. Trédaniel et al also fail even to mention the possibility that a threshold dose might exist.

5.14.8 Cessation of exposure

When examining whether any association is causal or not, evidence relating to reduction of risk given reduction of exposure is often considered very important. Trédaniel et al fail to make it clear that no such evidence exists here.

5.15 Public health impact

A number of the more recent papers by IARC have presented estimates of annual deaths per year due to ETS exposure.

In 1992, Boffetta and Saracci (9) referred to estimates from Canada, Australia and the United States, for the latter citing the estimate of 3820 lung cancer deaths a year from the draft, 1991, EPA report. For Europe, they noted that "a panel of experts has recently estimated the order of magnitude of lifetime excess risk of lung cancer due to domestic ETS exposure to be 1 per thousand persons habitually exposed. This risk corresponds, as a minimum, to several hundred deaths from lung cancer every year in the European Community."

The 1992 paper of Trédaniel et al (12) cited the estimates of Wells of US deaths in 1987, "3,000 cases of bronchogenic carcinoma, 11,000 other cancers, and 32,000 deaths due to heart disease."

The first 1993 paper of Trédaniel et al (13) cited estimates from a whole range of authors, including the EPA, Wells, Vainio, Wigle, Holman, Kawachi, Fong, Repace, Russell and Jarvis.

Similar references were made in the last 1994 paper of Trédaniel et al (18), from which the authors again stated that "it is, therefore, reasonable to assume that this risk corresponds, as a minimum, to several hundreds deaths, from lung cancer every year in the European Community."

These citations were always completely uncritical, never even suggesting weaknesses in any of these estimates, despite widely published criticisms. Papers

reporting much lower estimates are never cited. It is clear IARC have never actually carried out their own formal risk assessment.

6. Discussion and summary of conclusions

It is clear that the scientific quality of the various review papers produced by IARC is highly variable. Some of the papers are highly uncritical - for example, the 1989 paper by Trédaniel et al (5), when considering the data for children, presents a variety of tables listing associations reported in some studies, without making any attempt to discuss at all alternative explanations, seeming to regard evidence of association as evidence of a cause-and-effect relationship. Indeed some of the endpoints associated with ETS exposure are never given proper scientific consideration in any of the papers. Thus, the discussion of the evidence on heart disease is only very brief and superficial, even in the paper (12) giving most length to the subject; while the discussion of the evidence on health effects other than cancer in children (5, 12) is also very short and unsatisfactory. However, many of the papers, especially the longer ones, are much more critical than that, and a number of the more recent papers (9, 13, 16, 17, 18) contain sections concerning methodological limitations, sources of bias, and/or criteria for a causal association.

The most up-to-date and serious review papers are clearly those concerning cancer (13), possible effects of ETS exposure in pregnancy and childhood (16), non-neoplastic respiratory disease (17) and lung cancer (18). All are of a similar style and level of detail, presenting the results from the studies in tabular form with a brief textual description, discussing the various possibilities of bias, considering criteria for a causal association and then coming to a conclusion. While this general style is not an unreasonable one, there are a number of general limitations of the approach used. Thus:

(i) criteria are not given for how studies are to be selected for consideration or are rejected as methodologically inadequate,

(ii) weaknesses of specific studies are very rarely referred to, even though in some cases they are quite blatant,

(iii) criteria are not given for selecting data from the studies to be presented in their tables,

(iv) with the exception of the early Saracci and Riboli (6) paper, no attempt is ever made to carry out meta-analysis,

(v) no attempt is ever made to investigate whether results for different studies are

significantly heterogeneous, and, if so, why this should be,

(vi) although various sources of bias are considered, no formal calculations are ever made by IARC to try to judge their importance, though occasionally calculations made by others (e.g. with regard to bias due to smoker misclassification for lung cancer) are referred to,

(vii) it is often not apparent quite how the criteria for causation have been applied to reach the conclusions cited.

It is also clear that relevant facts are not always drawn attention to, and that alternative views of the evidence are often not referred to.

Despite these limitations the conclusions drawn by IARC regarding childhood cancer (16), non-neoplastic respiratory disease (17) and cancers other than the lung (13) are generally not unreasonable, though I have referred to certain weaknesses of these papers in my detailed comments.

The conclusions drawn in relation to lung cancer are, however, very much open to criticism, both in the main review (18), which states that "the causal association between ETS exposure and lung cancer now seems well-established" and in the review of data on effects of exposure early in life which states that "there is some consistency of association between ETS exposure in childhood and the risk of lung cancers in adulthood". Both papers are superficial and misleading. A major problem is that no attempt is made to collect together systematically data relating to specific indices of exposure. As a result the authors do not even seem to realize, let alone make clear to the reader, that the overall data show no association whatsoever of risk of lung cancer with workplace ETS exposure, with childhood ETS exposure or with ETS exposure in social situations. Although there is some evidence of an association of lung cancer with spousal smoking, strongly biased selection of data in their summary tables gives a misleading impression that it is stronger than it actually is. The importance of various sources of bias is under-estimated, no attempt being made to quantify the magnitude of their effects in comparison with the magnitude of the claimed association. No systematic attempt is made to see whether the spousal smoking relative risk estimates are consistently seen in various subsets of the data, so that it is not made clear that there is no real evidence of

an association with husband's smoking in (i) studies conducted in the USA, or in China, (ii) studies published after 1988, or (iii) studies of over 100 lung cancer cases. Failure to consider these important observations leads to misinterpretation of the overall evidence.

The section in the main paper on ETS and lung cancer on "proof of causation", which ends by concluding that "all the available data seem to fulfil at least to a reasonable degree, the criteria needed to accept a causal link between ETS and lung cancer among lifelong nonsmokers," is highly misleading. A review of the evidence should note inter alia that:

(i) there is no evidence of an association with any index of ETS exposure except for spousal smoking, where the evidence is weak and inconsistent,

(ii) the evidence of an association is not specific to a particular histological type,

(iii) the studies are subject to a number of potentially important biases,

(iv) there is limited evidence of a dose-response for spousal smoking but this too is subject to biases,

(v) the strength of the claimed association with spousal smoking is implausible bearing in mind the very small exposure to smoke constituents from ETS, and

(vi) there are no supportive animal experimental data.

Given all this, it is difficult to see how the "causal association between ETS exposure and lung cancer" can be considered "well-established".

Overall, one must have considerable concern when IARC fail to apply adequate scientific standards when reviewing the literature. It is hoped that any future review of possible effects of ETS exposure in the IARC monograph series, being conducted by a panel of independent experts, would come to a more reliable interpretation of the data.

Acknowledgements

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7. References

1 International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Tobacco smoking. Volume 38. IARC, Lyon, 1986.

2 Saracci R. Passive smoking and lung cancer. In: Zaridze D and Peto R (Eds): Tobacco: a major international health hazard. IARC, Lyon, 1986, 19-27.

3 Riboli E. Passive smoking and lung cancer: epidemiological evidence and ongoing international collaborative studies. Toxicol Lett, 1987, 35, 19-27.

4 Kalandidi A, Trichopoulos D, Hatzakis A, Tzannes S and Saracci R. Passive smoking and chronic obstructive lung disease. Lancet, 1987, ii, 1325-1326.

5 Trédaniel J, Hill C, Chastang CI and Hirsch A. Tabagisme passif et maladies respiratoires (French with English translation). Rev Mal Resp, 1989, 6, 109-120.

6 Saracci R and Riboli E. Passive smoking and lung: cancer current evidence and ongoing studies at the International Agency for Research on Cancer. Mutation Res, 1989, 222, 117-127.

7 Riboli E, Preston-Martin S, Saracci R, Haley NJ, Trichopoulos D, Becher H, Burch JD, Fontham ETH, Gao Y-T, Jindal SK, Koo LC, Le Marchand D, Segnan N, Shimizu H, Stanta G, Wu-Williams AH and Zatonski W. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. Cancer Causes Control, 1990, 1, 243-252.

8 Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracci R and Trichopoulos D. Passive smoking and diet in the etiology of lung cancer among nonsmokers. Cancer Causes Control, 1990, 1, 15-20.

9 Boffetta P and Saracci R. Fumée du tabac dans l'air ambiant et cancer du poumon [Environmental tobacco smoke and lung cancer] (English translation). Pollution Atmosphérique, 1992, April-June, 63-66.

10 Trichopoulos D, Mollo F, Tomatis L, Agapitos E, Delsedime L, Zavitsanos X, Kalandidi A, Riboli E and Saracci R. Active and passive smoking and pathological indicators of lung cancer risk in an autopsy study. JAMA, 1992, 268, 1697-1701.

11 Trichopoulos D, Mollo F, Tomatis L, Agapitos E, Delsedime L, Zavitsanos X, Kalandidi A, Riboli E and Saracci R. Active and passive smoking and pathological indicators of lung cancer - a report of limited value? [Letter] JAMA, 1993, 270, 1691.

12 Trédaniel J, Zalcman G, Boffetta P and Hirsch A. Le tabagisme passif. Effets sur la santé (French with English translation). Rev Prat (Paris), 1993, 43, 1230-1234.

13 Trédaniel J, Boffetta P, Saracci R and Hirsch A. Environmental tobacco smoke and the risk of cancer in adults. Eur J Cancer, 1993, 29A, 2058-2068.

14 Saracci R. Health effects of passive smoking in Europe (preliminary results). In: Vuylsteek K and Hallen M (Eds): Epidemiology. IOS Press, 1994, 48-53.

15 Trédaniel J, Boffetta P and Hirsch A. Faut-il reconnaître que le tabagisme passif est cancérogène? [Editorial] (French with English translation). Rev Mal Resp, 1994, 11, 443-445.

16 Trédaniel J, Boffetta P, Little J, Saracci R and Hirsch A. Exposure to passive smoking during pregnancy and childhood, and cancer risk: the epidemiological evidence. Paediatr Perinat Epidemiol, 1994, 8, 233-255.

17 Trédaniel J, Boffetta P, Saracci R and Hirsch A. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. Eur Respir J, 1994, 7, 173-185.

18 Trédaniel J, Boffetta P, Saracci R and Hirsch A. Exposure to environmental tobacco smoke and risk of lung cancer: the epidemiological evidence. Eur Respir J, 1994, 7, 1877-1888.

19 Pearce N, de Sanjose S, Boffetta P, Kogevinas M, Saracci R and Savitz D. Limitations of biomarkers of exposure in cancer epidemiology. Epidemiology, 1995, 6, 190-193.

20 Riboli E, Haley NJ, Trédaniel J, Saracci R, Preston-Martin S and Trichopoulos D. Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. Eur Respir J, 1995, 8, 285-290.

21 Riboli E, Haley NJ, De Waard F and Saracci R. Validity of urinary biomarkers of exposure to tobacco smoke following prolonged storage. Int J Epidemiol, 1995, 24, 354-358.

22 Breslow NE and Day NE. Statistical methods in cancer research. Volume 1 - The analysis of case-control studies. IARC Scientific Publications No 32. International Agency for Research on Cancer, Lyon, France, 1980.

23 Breslow NE and Day NE. Statistical methods in cancer research. Volume II - The design and analysis of cohort studies. IARC Scientific Publications No 82. International Agency for Research on Cancer, Lyon, France, 1987.

24 Wells AJ. An estimate of adult mortality in the United States from passive smoking. Environ Int, 1988, 14, 249-265.

25 Thornton AJ, Lee PN and Fry JS. Differences between smokers, ex-smokers, passive smokers and non-smokers. J Clin Epidemiol, 1994, 47, 1143-1162.

26 Lee PN. Environmental tobacco smoke and mortality. 1992, Karger, Basle.

27 LeVois ME et al. Publication bias in the environmental tobacco smoke/coronary heart disease epidemiological literature. Regulatory Toxicol Pharmacol, 1995, 21, 184-191.

28 Layard MW. Ischemic heart disease and spousal smoking in the National Mortality Followback Survey. Regulatory Toxicol Pharmacol, 1995, 21, 180-183.

29 Hirayama T. Passive smoking and cancer: the association between husbands smoking and cancer in the lung of non-smoking wives; in Kasuga H (ed): Indoor Air Quality. Int Arch Occup Environ Health Suppl. Berlin, Springer, 1990, pp 299-311.

30 Lee PN and Forey B. Misclassification of smoking habits as determined by cotinine or by repeated self-report - a summary of evidence from 42 studies. J Smoking-Related Disorders. In Press.

31 Lee PN and Forey BA. Misclassification of smoking habits as a source of bias in the study of environmental tobacco smoke and lung cancer. Statistics in Medicine. In Press.

32 Armstrong BK, White E and Saracci R. Principles of exposure measurement in epidemiology. Monographs on Epidemiology and Biostatistics, 21, Oxford University Press, 1994

33 Lee PN. Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer. A review of the published data. APMIS, Supplement 45, 1994, 102, 1-42

34. Lee PN. "Marriage to a smoker" may not be a valid marker of exposure in studies relating to environmental tobacco smoke to risk of lung cancer in Japanese non-smoking women. Int Arch Occup Environ Med. In Press.

35. Phillips K et al. Assessment of personal exposures to environmental tobacco smoke in British nonsmokers. Environ Int, 1994, 20, 693-712.

36. Reif JS et al. Passive smoking and canine lung cancer risk. Am J Epidemiol, 1992, 135, 234-239.

TABLE 1

The 20 papers reviewed and the areas they consider

Ref	First author (year)	Possible health effects in adults				Possible effects in children		IARC studies	
		Lung Cancer	Other Cancer	Heart Disease	Non-neo-plastic Resp Dis	Childhood Cancer	Other Diseases	Cotinine	Lung Cancer
2	Saracci (1986)	✓							
3	Riboli (1987)	✓					✓	✓	
4	Kalandidi (1987)				✓				
5	Trédaniel (1989)	✓		✓			✓		
6	Saracci (1989)	✓						✓	✓
7	Riboli (1990)			✓				✓	
8	Kalandidi (1990)	✓							
9	Boffetta (1992)	✓					✓		
10	Trichopoulos (1992)	✓							
11	Trichopoulos (1993)	✓							
12	Trédaniel (1993)	✓	✓	✓	✓		✓		
13	Trédaniel (1993)	✓	✓						
14	Saracci (1994)								✓
15	Trédaniel (1994)	✓					✓		
16	Trédaniel (1994)	✓				✓			
17	Trédaniel (1994)				✓				
18	Trédaniel (1994)	✓							
19	Pearce (1995)							✓	
20	Riboli (1995)							✓	
21	Riboli (1995)							✓	

TABLE 2

A comparison of relative risks for spousal smoking
cited by various sources
Earlier studies

Study/ year		Sex	Saracci & Riboli (6)	Lee	EPA Crude	EPA Adjusted	Trédaniel et al (18)
Garfinkel	1981	F	1.18	1.17	-	1.17	1.27,1.10
Chan	1982	F	0.75	0.75	0.75	-	0.75
Correa	1983	F	2.03	2.07	2.07	-	1.5,3.1
		M	2.29	1.97	-	-	-
Trichopoulos	1983	F	2.11	2.08	2.08	-	1.9,1.9,2.5
Buffler	1984	F	0.80	0.80	0.81	-	Omitted
		M	0.50	0.51	-	-	Omitted
Gillis	1984	F	1.00	Superseded by results of			
		M	3.25	Hole (1989) study			
Hirayama	1984	F	1.63	1.45	1.53	1.64	1.4,1.4,1.6,1.91
		M	2.25	2.25	-	-	-
Kabat	1984	F	0.79	0.79	0.79	-	0.79
		M	1.00	1.00	-	-	1.00
Garfinkel	1985	F	1.23	1.23	1.31	-	1.2,1.2,1.1,2.1
Wu	1985	F	Omitted	1.20	1.41	1.20	1.4,1.2
Akiba	1986	F	1.48	1.50	1.52	1.50	1.3,1.5,2.1
		M	2.45	1.80	-	-	-
Lee	1986	F	1.03	1.00	1.03	-	1.03
		M	1.30	1.30	-	-	-
Humble	1987	F	2.16	2.20	2.34	2.20	See Table 3
Koo	1987	F	1.54	1.64	1.55	1.64	1.83,2.56,1.21
Pershagen	1987	F	1.27	1.20	1.28	1.20	1.00,3.20
Knoth	1983		Omitted	Omitted	Omitted		Omitted
Miller	1984		Omitted	Omitted	Omitted		Omitted
Ziegler	1984		Omitted	Omitted	Omitted		Omitted
Sandler	1985		Omitted	Omitted	Omitted		Omitted
Dalager	1986		Omitted	Omitted	Omitted		Omitted

TABLE 3

A comparison of relative risks for spousal smoking
cited by various sources
Later studies

Study/ year		Lee	EPA Crude	EPA Adjusted	Trédaniel et al (13,15,18)	Comment on index used by Trédaniel et al or reason for omission
Brownson	1987	1.68	1.82	1.68	1.68	Same as Lee and EPA
Gao	1987	1.19	1.19	1.34[1]	1.70	High exposure (40+ years)
Humble	1987	2.20	2.34	2.20	2.60	Estimate for sexes combined
Lam	1987	1.65	1.65	-	1.65	Same as Lee and EPA
Butler	1988	2.02	2.45	2.02	Omitted	Major methodological limitations
Geng	1988	2.16	2.16	-	Omitted	Major methodological limitations
Inoue	1988	2.25	2.55	2.54	Omitted	Major methodological limitations
Lam	1988	2.01	2.51[2]	-	Omitted	Very limited information
Shimizu	1988	1.08	1.08	-	1.10,4.00,3.20	Last 2 estimates relate to smoking by mother and husband's father
Hole	1989	2.41	2.27	1.99	2.41	Same as Lee
Svensson	1989	1.26	1.26	1.40[1]	2.10	Exposure index at home and at work
Janerich	1990	0.75	0.86	0.93/0.44[3]	1.11	High adulthood exposure (75+ smoker years)
Kalandidi	1990	2.11	1.62	1.92	1.92	Same as EPA
Sobue	1990	1.13	1.06	1.13	1.50	Household member smoking in adulthood
Wu-Williams	1990	0.70	0.79	0.70	0.70	Same as Lee and EPA
Joeckel	1991	2.27	Omitted	Omitted	Omitted	Not cited by Trédaniel
Liu	1991	0.77	0.74	0.77	Omitted	Major methodological limitations
Fontham	1991/4[5]	1.29	1.32	-	1.29	Same as Lee
Brownson	1992	1.00	Omitted	Omitted	1.80	Heavy reported adulthood exposure
Stockwell	1992	1.60	Omitted	Omitted	1.60	Same as Lee
Liu	1993	1.66	Omitted	Omitted	2.90	Heavy spousal exposure
Du	1993	1.09	Omitted	Omitted	Omitted	Recent study
Wang	1994	0.91	Omitted	Omitted	Omitted	Recent study
Layard	1994	0.58	Omitted	Omitted	Omitted	Recent study
Kabat	1995	1.08	Omitted	Omitted	Omitted	Recent study
Katada	1988	Omitted	Omitted	Omitted	Omitted	Major methodological limitations
Chen	1990	Omitted	Omitted	Omitted	Omitted	Major methodological limitations
Lan	1993	Omitted	Omitted	Omitted	Omitted	Recent study
Miller	1994	Omitted	Omitted	Omitted	Omitted	Recent study

[1] Estimated by EPA from data by level
[2] EPA data for different exposure index
[3] Lee estimate is weighted average of estimates for two subsets
[4] Kalandidi presented 2 adjusted estimates
[5] EPA estimate from 1991 paper, others from 1994 paper