RESEARCH PAPER

Challenging the epidemiologic evidence on passive smoking: tactics of tobacco industry expert witnesses

John A Francis, Amy K Shea, Jonathan M Samet

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See end of article for authors' affiliations

Correspondence to: Professor Jonathan M Samet, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Suite W6041, Baltimore, MD 21205, USA; jsamet@jhsph.edu

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Objective: To analyse the statements given by tobacco industry defence witnesses during trial testimonies and depositions in second-hand smoke cases and in parallel, to review criticisms of epidemiology in industry-funded publications in order to identify strategies for discrediting epidemiologic evidence on passive smoking health effects.

Methods: A collection of depositions and trial testimony transcripts from tobacco industry-related lawsuits filed in the United States during the 1990s, was compiled and indexed by the Tobacco Deposition and Trial Testimony Archive (DATTA). Statements in DATTA made by expert witnesses representing the tobacco industry relating to the health effects of passive smoking were identified and reviewed. Industry-supported publications within the peer-reviewed literature were also examined for statements on exposure misclassification, meta-analysis, and confounding.

Results: The witnesses challenged causation of adverse health effects of passive smoking by citing limitations of epidemiologic research, raising methodological and statistical issues, and disputing biological plausibility. Though not often cited directly by the witnesses, the defence tactics mirrored the strategies used in industry-funded reports in the peer-reviewed literature.

Conclusion: The tobacco industry attempted to redirect the focus and dialogue related to the epidemiologic evidence on passive smoking. This approach, used by industry experts in trial testimony and depositions, placed bias as a certain alternative to causation of diseases related to passive smoking and proposed an unachievable standard for establishing the mechanism of disease.

For a half century, epidemiological evidence on active and passive smoking has had a central and pivotal role in driving policies to control tobacco use. The findings of epidemiological research, along with toxicological studies of tobacco smoke and its components, have repeatedly supported conclusions that active and passive smoking cause specific diseases as well as non-specific, but adverse, health effects.^{1–3} The classification of smoking as a cause of disease in smokers and non-smokers has had powerful implications for disease prevention and also for establishing a foundation to prove the liability of the tobacco industry, which has produced, marketed, and promoted use of this disease-causing product.

Because of the powerful consequences of epidemiological studies, their findings have long been questioned by the tobacco industry and its hired consultant scientists with the intent of maintaining apparent controversy around research results.⁴ The tactics largely followed those used by researchers in considering whether an association can be attributed to a causal process or to alternatives to causation—the play of chance or to bias arising from confounding, participant selection, or misclassification. These alternatives were given lengthy consideration in the 1964 report of the Surgeon General⁵ and have received close attention in subsequent reports of the Surgeon General and of other expert bodies as the list of diseases caused by smoking has lengthened.²

In its decades-long attack on the findings of epidemiological research, the tobacco industry—through its scientists and consultants—has emphasised persistently various biases as explaining observed associations of smoking with disease, initially using this strategy for active smoking and then for passive smoking (more commonly labelled by the tobacco industry as environmental tobacco smoke or ETS). Research in the industry documents has shown that the industry has made comprehensive efforts to change the language and

dialogue on the epidemiologic evidence.^{6–9} The line of argument has been complemented by a systematic attempt to diminish the significance of epidemiological findings¹⁰ in order to prevent regulation and avoid litigation.^{10–13} The industry has long advanced the proposition that epidemiological studies can only demonstrate an “association” that can be classified as causal only with a confirming animal model and a demonstrated “mechanism”.

The focus of this study was to document the approach used during depositions and trial testimony in cases related to secondhand smoke and compare the methods of attack to industry-funded publications. The parallel story of the industry strategy on secondhand smoke can be found throughout the tobacco control literature.^{6–9 10 14}

METHODS

The information on which this review is based came from the Tobacco Deposition and Trial Testimony Archive (DATTA) and from publications in the peer-reviewed literature. The Tobacco DATTA is a collection of depositions and trial testimony transcripts from tobacco industry-related lawsuits filed in the United States during the 1990s, and catalogued by the Center for Tobacco Use Prevention and Research (www.tobaccodocuments.org).¹⁵ Before analysis, each document in the database had been indexed and coded topically into 11 primary themes (for example, health consequences of passive smoking) as designated by DATTA in order to identify and extract relevant information. Excluded from the archive

Abbreviations: CIAR, Center for Indoor Air Research; DATTA, Tobacco Deposition and Trial Testimony Archive; EPA, Environmental Protection Agency; ETS, environmental tobacco smoke; IARC, International Agency for Research on Cancer; NHANES, National Health and Nutrition Examination Survey; ORNL, Oak Ridge National Laboratory; OSHA, Occupational Safety and Health Administration

were administrative hearings, such as that held by the Occupational Safety and Health Administration (OSHA) in 1994–1995, and lawsuits filed in other countries.

Using the categorisation of trials and depositions established by DATTA, we identified those individuals who had represented the tobacco industry in cases related to the health effects of passive smoking. In reviewing these cases, we selected for further examination those frequent witnesses whose testimony related directly to the epidemiological evidence on secondhand smoke.

The selected trials and depositions were read, examined, and further indexed for statements relating to secondhand smoke. Based on the authors' initial review, the statements were grouped into nine categories: (1) limitations of epidemiology—for example, epidemiologic evidence only suggests hypotheses for further study; (2) low relative risk or "weak effects" of secondhand smoke; (3) confounding, with research failing to account for possible confounders; (4) misclassification, including active smoking status and exposure to secondhand smoke; (5) lack of biological plausibility; (6) small sample sizes of studies, statistical significance and imprecise measures of effect; (7) limitations of meta-analysis; (8) publication bias; and (9) limitations of animal studies. For the purposes of presentation and consolidation within this manuscript, these categories were grouped by specific research topics: (1) limitations of epidemiology (causation and weak effects); (2) misclassification and confounding associated with individual studies; (3) limitations of pooling of information (meta-analysis and publication-bias); and (4) lack of animal models and questioning of biological plausibility.

In parallel, based on the knowledge and experience of the authors, we searched for industry-supported publications within the peer-reviewed literature on misclassification, meta-analysis, and confounding, particularly in relation to secondhand smoke. Depositions and trials were examined for the specific mention of authors or publications relating to the witness's statements. The statements referenced, given by an expert witness during a trial or deposition, have been italicised in this report.

RESULTS

There were 287 referenced documents relating directly to secondhand smoke within DATTA. Of those, seven expert witnesses whose testimony related to the epidemiological evidence on secondhand smoke were identified, and a total of 38 depositions and testimonies were reviewed. Four of the seven experts were employed by major tobacco companies (Brown & Williamson, Philip Morris, Lorillard, and RJ Reynolds) either directly or as consultants, and the remaining three held professorial positions at various US universities (table 1). Their areas of expertise were statistics, pharmacology, toxicology, analytical chemistry, and epidemiology.

Reviewed depositions and trial testimony included those in the 1990s which were named as: (1) the state attorney general cases; (2) class action cases (for example, *Engel v. R.J. Reynolds Tobacco Co*); (3) individual disease cases; (4) third-party reimbursement cases; and (5) miscellaneous cases. The major trials in which each expert made statements in reference to secondhand smoke within either deposition or testimony are described in table 2.

Table 1 Description of experts and the number of reviewed depositions/testimonies regarding secondhand smoke, as identified by DATTA

Name	Expertise	Employment/affiliation	Depositions	Trials
Appleton, Bernard Scott	MS Nutrition, PhD Environmental Toxicology	Director of Regulatory Affairs, Brown & Williamson (1991)	1	5
Bradley, Edwin Luther	PhD, Statistician and Biostatistician	Professor Emeritus, University of Alabama-Birmingham. Consultant at Quantitative Research Associates	1	3
Carchman, Richard Allen	PhD, Pharmacologist	Consultant to Philip Morris, Professor in the department of pharmacology, toxicology and biostatistics, Medical College of Virginia	7	6
Coggins, Christopher	PhD, Toxicologist and Epidemiologist	Senior VP of Science and Technology for Lorillard. Statistician for Battelle. Toxicologist for RJR	2	2
Jenkins, Roger A	PhD Analytical Chemistry	Oak Ridge National Laboratory	2	3
Levy, Paul	ScD, Statistician and Epidemiologist	University of Illinois-Chicago	0	2
Ogden, Michael Wayne	PhD Analytical Chemistry	Principal scientist, RJR	3	1

Table 2 Description of trials

Trials	Description	Experts reviewed
Dunn (Wiley) v. RJ Reynolds	Individual products liability action	Appleton, Carchman, Coggins, Jenkins, Levy, Ogden
Falise v. American Tobacco Co	Third party reimbursement, smoking and asbestos exposure	Appleton
Broin v. Philip Morris Inc	National class action on behalf of flight attendants injured by secondhand smoke	Appleton, Bradley, Carchman, Coggins, Jenkins, Ogden
Engle v. R.J. Reynolds Tobacco Co Tobacco Cases II	Class action for smoker injuries Plaintiff State of California, consolidated with Philip Morris Inc, General Cigar Co, Brown and Williamson Tobacco Corp, and Tobacco Exporters.	Appleton Carchman, Coggins, Jenkins, Ogden
Tompkin v. American Brands Inc	Individual/personal injury	Coggins, Bradley
Oklahoma v. R.J. Reynolds	Oklahoma Medicaid	Ogden
Butler v. Philip Morris Inc	Wrongful death	Bradley, Carchman
Small v. Lorillard Tobacco Co	Class action litigation, consolidated with Hoskins, Hoberman, Frosina, Zito	Carchman
Schwarz v. Philip Morris	Products liability case. Individual smoker	Carchman
Blue Cross of New Jersey v. PM	Third-party reimbursement	Carchman

LIMITATIONS OF EPIDEMIOLOGY

Causation

In reviewing these transcripts, we first identified the general approach of diminishing the findings of epidemiological studies, which has two main elements: (1) epidemiological studies and their findings cannot lead to a causal conclusion; and (2) epidemiology cannot be used credibly to study the biological mechanisms associated with disease. These propositions were raised by witnesses Drs Appelton, Bradley, Charchman, and Coggins.

The tobacco industry and its experts have consistently raised the limitations of epidemiological studies as illustrated by Dr Bradley: *"Epidemiological studies by themselves cannot determine causation. They can only establish association. But that's – if you think of causation is like a table, it has many legs to it. And one of these legs is the epidemiological study. And so you have to establish some type of association before you can have causation... If the studies show an association that doesn't imply causation, but if the studies show no association then there can be no causation."*¹⁶

The defence witnesses attempted to build their arguments by separating epidemiologic research from scientific research. Dr Appleton stated: *"My assessment was more scientifically based. I looked at it from a more scientific point of view and used different assessment criteria, which included a much broader range of scientific criteria."*¹⁷ The scientific purview of epidemiologic methods was framed as limited, in the words of Dr Coggins, to "generating hypotheses".¹⁸

*"I can only make my scientific comment. And that is there are a large number of epidemiological studies that have given inconsistent results that have shown a statistical association between lung cancer and smoking. Because epidemiology cannot prove causation, in my mind, epidemiology can only generate hypotheses which can then be tested using the scientific method. But epidemiology is incapable of teasing out individual factors within a composite lifestyle."*¹⁸

The witnesses' statements are based on the premise that no true proof of causation exists without evidence from properly conducted scientific research establishing the actual mechanisms linking exposure to disease.

Weak effects

One repeatedly used industry tactic has been to dismiss epidemiologic studies of effects so small as to be pejoratively labelled "weak". The increased risk of lung cancer in never smokers associated with ETS exposure has been labelled repeatedly and consistently as representing a "weak effect" by the industry, both in publications by consultants and in testimony.^{19–22} For lung cancer, the magnitude of the increased risk, approximately 25% when comparing non-smokers married to smokers with non-smokers married to non-smokers, is far lower than the approximately 2000% increased risk of lung cancer in active smokers, compared to non-smokers. While bias is of greater concern for lower relative risk estimates as an alternative to causation, we would not anticipate a high relative risk for passive smoking, given knowledge of the carcinogenic components of ETS and the doses received by non-smokers. Review groups and the resulting expert reports, since the 1986 Report of the Surgeon General, have concluded repeatedly that ETS causes lung cancer in non-smokers, basing these conclusions not only on the evidence of passive smoking but also the evidence of active smoking and on the extensive information on the components of ETS.²³

Within the trials and testimonies examined, experts argued that with relative risks lower than 2.0 (for example, a risk

increase less than 100%), epidemiological evidence should be set aside in considering causality. *"The general standard is the risk must exceed two before you can consider it is truly a possible measure of association between the disease and the exposure."*²⁴

Publications from industry-supported authors have given similar conclusions, claiming that relative risks below two are "problematic" as a result of a high likelihood of being due to significant confounding and bias.^{25–28} Dr Peter N Lee, a long-time consultant for the tobacco industry, linked his conclusion on this matter to a publication of the International Agency for Research on Cancer (IARC) which states "relative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor".²⁹ This statement was made in an individually authored contribution to a monograph on case-control studies. Dr Ernst Wynder, a pioneer in tobacco control research but who later received support from the tobacco industry,³⁰ repeatedly took a sceptical stance on the evidence on second-hand smoke and lung cancer, citing his concerns about the value of epidemiological methods for relative risks in the range observed.^{31–33} He stated, for example, that: "It is not easy to define quantitatively what is meant by 'weak,' but Cornfield's view that any relative risk of under 3 might be considered weak is reasonable."³⁴ Today, the industry-supported¹¹ website (www.junkscience.com) also believes we should "ignore relative risks between 0.50 and 2.0".³⁵

Other defence experts supported the attempt to build controversy around the relative risks observed for passive smoking by making such statements as: *"Generally, in epidemiology, a relative risk below 2 is considered a weak association."*³⁶ Dr Appleton concluded that the Environmental Protection Agency's "relative risk of 1.19 is considered very low" in comparison to greater relative risks of breast and colon cancer associated with dietary fat.¹⁷ These propositions were also echoed by Dr Coggins: *"...odds ratios below 2 or 3 are meaningless"*,¹⁸ and Dr Charchman: *"Less than five carries with it, in my mind, a series of further subdivisions with somewhere between two and five being weak and less than two being weak to marginal."*³⁷

MISCLASSIFICATION

Misclassification of exposure was raised repeatedly, with defence experts questioning the exposure assessment aspect of study design and the resulting conclusions. Several forms of misclassification were proposed, all considered to be substantial limitations of the epidemiological findings: (1) misclassification of active smokers, either current or former, as non-smokers; (2) random reporting error when describing second-hand smoke exposure; and (3) biased reporting of secondhand smoke exposure, leading to upwardly biased risk estimates. Witnesses testified that results were likely to be biased based on exposure classification by questionnaires, the principal method in the epidemiologic studies. They also implied that disease status would influence self-reported data and subject's perceived—and not actual—exposure (table 3).^{18 36 38 39} These statements made by defence witnesses regarding misclassification reflect a long-used industry tactic which is evident in peer-reviewed industry publications.

Dr Lee repeatedly raised concerns about misclassification of smoking status. Beginning in the 1980s, his publications had the apparent goal of refuting research showing that non-smoking women married to smokers were more likely to develop lung cancer than women married to never smokers.^{40–42} In 1987, Dr Lee addressed potential misclassification bias from use of self-reported active smoking status by comparing reported smoking status with level of salivary cotinine.⁴² In these publications, as documented by Hong and Bero,⁴⁰ Dr Lee attempted to develop evidence that could be used to attribute the positive findings of Dr Hirayama's

Table 3 Trial quotes related to misclassification

Witness	Date	Trial	Quote
Bradley	6 October 1997	Broin v Philip Morris	"Most of the studies that are done with ETS take a group of people that are supposed to be non-smokers and that are exposed, and measures their lung cancer risk. And to evaluate whether they are non-smokers, generally they just ask them a question, Are you a smoker or not. And if they don't truthfully answer that question, they're going to be misclassified as a non-smoker when in fact they are a smoker."
Coggins	22 May 1997	Broin v Philip Morris	"Well, if you put a non-smoker in an exposed group, and the person is actually a smoker and they end up getting lung cancer, then...the relative risk for active smoking is fairly high, so that confounds the results, and it's unclear[a]s to whether the exposure is due to ETS or the active smoking." "The only measure of exposure was a single question asked of these nurses in 1982. That is the only measure of exposure. And as we know, questions are notoriously unreliable. I recall the home data showed no effect. The work data showed no effect. It is a statistical combination of the two I think that showed a marginal effect." "[W]e have no estimates of exposure. We have no idea whether any of these people were ever exposed. And this fudging of data together to increase the numbers I think scientifically is not a justifiable step. If you are interested in spousal smoking, look at spousal [smoking]. If you are interested at workplace [sic], look at workplace. Combining the two to get a larger value is a statistical misstep I think."
Jenkins	15 August 1997	Tobacco Cases II	"Because sometimes people have a sense of the kind of environment that they work, but, in fact, they may not accurately report that environment."
Levy	9 March 1998	Dunn v RJ Reynolds	"[I]f in the case/control study, a case is more likely to remember that exposure to environmental tobacco smoke than a control, which is not altogether unlikely because they're more sensitized to it. It would again tend to raise the relative risk."

cohort study to misclassification of active smoking status.⁴³ Hirayama's 1981 paper, one of the first on passive smoking and lung cancer risk, reported a nearly twofold increase in the risk of lung cancer for non-smoking women married to smokers, compared to those married to non-smokers.⁴³ In an article published 14 years after Dr Hirayama's first report, Dr Lee provided findings of a separate population that were intended to again raise questions about the possible consequences of misclassification bias. In Dr Lee's study, of the 400 married women completing questionnaires and providing urine samples, 106 were classified as current smokers on the basis of cotinine measurements; 22 of the 106 reported being a never-smoker. Dr Lee indicated that under reporting of active smoking might have biased Hirayama's results. Because current smokers were more likely to live with a currently smoking husband, the increased risk attributed to passive smoking was postulated to reflect uncontrolled and unreported active smoking.⁴⁴

Dr Jenkins, a toxicologist and chemist working for Oak Ridge National Laboratory (ORNL), both carried out research and served as an industry witness. His research was supported by the industry-sponsored Center for Indoor Air Research (CIAR) through specially channelled funding to carry out a substantial series of studies.⁴⁵ ORNL is a contract laboratory of the Department of Energy established in 1943, supported by federal, state, and private funds. Much of Dr Jenkins' recent research and publications have focused on measuring tobacco smoke exposure and estimating the risk of measured exposure.⁴⁶⁻⁶³ Based on his publications, Dr Jenkins' statements in testimony addressed misclassification and doses of ETS.

Dr Jenkins published a number of papers based on the CIAR-sponsored study, commonly referred to as the "Sixteen Cities" study,⁵⁶ and he frequently referred to its findings during trial testimony.⁶⁴ In this study, approximately 100 subjects per city wore samplers for collection of respirable particulate matter over a 24-hour period. Dr Jenkins compared "true smoking workplaces" with "true smoking homes" and concluded that workplace exposures were less than home exposures, and less than assumed by OSHA's 1994 risk assessment.⁵⁶ Dr Jenkins also considered the elevated estimates to be an indicator of workplace exposure misclassification. "While numerous subjects observed people smoking in their workplaces, in fact, many of the workplaces had some type of smoking restriction imposed. The restrictions would lower the ETS exposure of subjects occupying

areas which would otherwise be considered as smoking workplaces."⁵⁶

On 23 September 1997, in the court case Broin v. Philip Morris, plaintiffs' attorneys were unsuccessful in their attempt to exclude the 16 Cities paper from testimony.⁶⁵ Referring to his study, Dr Jenkins stated: "*The essential conclusion there was that...exposures in the homes can typically be two to more times greater from spousal smoking than exposures in the workplace.*"⁶⁵ Dr Jenkins also questioned the exposures of nurses and flight attendants to ETS, testifying that their exposures were lower than in typical workplace environments and significantly lower than in smoking households.⁶⁴⁻⁶⁶

CONFOUNDING

In addressing the association of second-hand smoke exposure with increased risk for adverse effects, including lung cancer, defence experts raised confounding repeatedly as an alternative to causation. This strategy parallels the attempt used decades earlier by the tobacco industry to discredit the powerful findings on active smoking. By definition, a confounder must fulfil the following three conditions. The factor must: (1) cause the disease in the unexposed; (2) be associated with the exposure; and (3) not be in the causal pathway of the exposure.⁶⁷ If confounding is not appropriately controlled, it may increase or decrease a risk estimate, in relation to the true value. When considering lung cancer in never smokers, the principal possibility for confounding lies in occupational agents or other high-level environmental exposures, such as radon.

The apparent validity of relative risk estimates will diminish as the number of potential confounding variables lengthens. Attacking the epidemiologic conclusions by proposing confounding as the alternative to causation involves creating lists of potential confounders that include factors not meeting the criteria for confounding and then questioning whether they were controlled for in a study or whether the control was adequate. Many "confounders" have been nominated, even when the evidence linking them to lung cancer risk in never smokers was scant. As a result, the list of "potential" confounding variables, as suggested by industry experts, has become quite lengthy and includes alcohol consumption, cooking exposure, diet, family history, level of education, obesity, occupation, radon exposure, and socioeconomic status.⁶⁸

Expert defence witnesses, such as Dr Coggins, spoke repeatedly of the problem of confounding. "*It is well known*

Table 4 Trial quotes related to confounding

Witness	Date	Trial	Quote
Appleton	7 October 1997	Broin v. Philip Morris	"[Koo and Kabat] also concluded that these dietary differences may very well account for the small association that seems to exist in some of these studies of non-smoking spouses with smoking spouses. They even draw the conclusion that this seems to be at variance with the EPA report." "Smokers tend to have diets that tend to increase their risk of lung cancer. And this examined the issue of whether or not non-smokers who live with a smoker also share those same lifestyle and dietary habits."
Bradley	6 October 1997	Broin v Philip Morris	"For example, if these three items here have been shown to be related both to an increased incidence of lung cancer and to someone smoking in the home; that is, a diet composed of high fat foods, lifestyle factors such as lack of exercise, and also a low fruit and vegetable diet. So those three factors are all related with an increase in lung cancer, and are also associated with people that smoke."
Appleton	13 March 1998	Dunn v. RJ Reynolds	"Dietary fat is, in fact, associated with lung cancer. There are epidemiological studies that link dietary fat to lung cancer and also red meat is linked to colon cancer."
Levy	9 March 1998	Dunn v. RJ Reynolds	"In reference to controlling for confounders, "Some of them did for some confounders, some of them did for other confounders, some of them did no control for confounders. As far as I remember, none of them controlled completely for—well, it's hard to control—none of them controlled for all of the confounders." "[L]ung cancer in women; such as diet, radon, previous history of lung disease, that type of—the type of lifestyle and previous disease exposure." "[B]ased on the presence of bias and confounding on the weakness of the association that makes them especially fragile with respect to this...they give very little or no evidence of a causal relationship between environmental tobacco smoke and lung cancer."

there are over 200 potential confounders."¹⁸ In the industry-supported publications, conclusions on confounding were congruent to statements by the expert defence witnesses (table 4).^{17 36 38 69} In trial testimony, as identified by Appleton, Bradley, Coggins, Carchman, and Levy, listings of possible confounding variables included low socioeconomic status, alcohol consumption, diet composed of high fat foods, lifestyle factors such as lack of exercise, low fruit and vegetable diet, and radon exposure. Long-time Philip Morris scientist Dr Carchman stated the following in his testimony:

"...there have been publications based in the United States, on CDC data, called the NHANES database, that shows that nonsmoking women that live with smoking men adopt many of the lifestyle habits of their smoking spouse. That means they don't eat a lot of fresh fruits and vegetables. They eat a lot of meats high in saturated fats. And they generally don't exercise. There are a whole series. Why is this important? Because each of these things that I just mentioned all contribute to a variety of diseases, including lung cancer. So you have to control. Otherwise, you're comparing apples with oranges."⁷⁰

The NHANES (National Health and Nutrition Examination Survey) analyses referenced in the trials were, in fact, supported by CIAR.⁷¹ The 1995 peer-reviewed publication by Matanoski *et al* reached conclusions on confounding similar to the comments of defence witnesses:

"Because diet may be a proximal factor in the causal chain of disease etiology that is related to low socioeconomic conditions, the persistence of these dietary effects after correction for education is noteworthy... Some of the relations between the variables may not be simple. Thus, exposure to household tobacco smoke may not represent just a single exposure but a complex of factors many of which, such as low vitamin intake and high alcohol intake, have been shown to influence the risk of cancer."⁷²

Dr Matanoski concludes in this study: "Further studies should investigate the role of both diet and passive smoking to determine the contribution of each in the development of lung cancer."

Another industry-supported scientist, Dr Linda Koo in Hong Kong, also published on second-hand smoke and confounding. Throughout the 1980s and 1990s, Dr Koo participated in the industry's "consultants program" in Asia, targeting second-hand smoke. During this time, without acknowledging ties to the tobacco industry, Dr Koo aided the industry's position through research and related publications addressing the role of confounding variables in contributing to increased lung cancer risk associated with passive smoking.⁷³ Dr Koo and colleagues stated that:

"It has been shown that for each air pollutant, the quality of the diet among the exposed coincided with their lung cancer risk patterns, i.e. poorer diets for ETS exposed, better for those with incense exposure, and relatively better for the lung cancer cases with more cooking exposures (because the quality of diet was significantly poorer among the controls)."⁷⁴

An additional tactic using confounding claims that studies have failed to account for all possible confounders. In a study supported by the Tobacco Institute on workplace and spousal exposure in 1994, LeVois and Layard²⁰ stated:

"In fact, nearly every potential confounder that has been identified is likely to inflate a risk estimate derived from spousal smoking data. None of the ETS-lung cancer epidemiologic studies adequately accounts for the effects of most of the known potential confounders."²⁰

META-ANALYSIS

Use of meta-analysis was a target for both trial experts and peer-reviewed reports generated with support by the tobacco industry. Meta-analysis had been used with regard to secondhand smoke exposure and lung cancer risk, as well as for other health outcomes, to combine the evidence from individual studies and to generate a more precise estimate of risk than was available from the individual studies. Defence experts raised the limitations of the methodology, particularly for associations which were considered "weak". The emphasis on criticising meta-analysis likely came initially from its use by the US Environmental Protection Agency's (EPA) 1992 risk assessment.⁷⁵ Of the critiques submitted to the EPA's Scientific Advisory Board as it evaluated the risk

assessment, 71% came from the tobacco industry.⁷⁶ As a result of confounding, misclassification, publication bias, and discrepancies within or between studies, defence witnesses argued that meta-analysis can “give very little or no evidence of a causal relationship”.³⁶

The testimony regarding use of meta-analysis attempted to create and sustain controversy around conclusions that were based on pooled evidence. Dr Levy states: “My opinion is that on the basis of these studies, one cannot...conclude that there is a relationship between environmental tobacco smoke and lung cancer.”³⁶ Dr Levy also answered questions concerning the bias produced in the EPA report from the exclusion of known publications.

Q. “Now, had the EPA included in its meta-analysis all 13 studies that were available to it, would that have changed the results of its meta-analysis?”

A. “I believe it would have...”

Q. “And how would it have changed the results, Doctor?”

A. “...if they had used 13 available at the time...of publication, they would have found a non-significant result.”⁷⁷

Dr Coggins stated that he was “very critical of the approach used by the EPA in combining studies. The studies were very different and should never have been combined, in my opinion.”⁷⁸ He also questioned the research methodologies and inconsistent results of the publications used: “I think an odds ratio of 1.3 replicated 10 or 15 times would be a hypothesis worth testing further. That is all I think epidemiology can do. But if you have 10 studies that have odds ratios...spread all over the place with no consistency, I would say there isn’t even a hypothesis.”

This method of attack has been well-documented in publications supported by the tobacco industry. In the 1980s, five industry-supported peer-reviewed publications challenged the methodologies of meta-analysis (table 5^{79–82}) and questioned the conclusions of both the National Research Council’s 1986 report⁸³ and the EPA’s draft (1990) and final risk assessment report.⁷⁵ These publications cite the failure to account for publication bias, the inability to re-estimate relative risks from raw data, and questionable statistical methods as limiting factors of meta-analysis.

ANIMAL MODELS

To manage the implications of increasing epidemiologic evidence relating passive smoking to lung cancer in the

1980s, the tobacco industry attempted to minimise epidemiology as showing merely associations with disease and proposed the need for consistent toxicologic and mechanistic evidence before inferring causality. This approach mirrored tactics long used for active smoking.⁸⁴ The standard for causation proposed seems to emphasise an unachievable level of mechanistic certainty. Animal toxicology and other laboratory data are complementary to epidemiological evidence but not in the rigid paradigm proposed by the industry. In fact, as for active smoking, the production of lung cancer in passively exposed animals has proved challenging and studies at typical concentrations of second-hand smoke at which humans are exposed cannot be carried out. However, injury short of malignancy can be investigated and biomarker studies have been conducted.

We have now learned that the industry itself supported research intended to maintain its claims and criticisms about second-hand smoke, but the industry’s ties to this research were often undisclosed and findings inconsistent with industry positions were not reported. For example, animal studies on passive smoking were conducted by a Philip Morris German research facility (INBIFO) during the 1980s, but the connection of Philip Morris with INBIFO was kept secret. The studies showed harmful effects,⁸⁴ but beginning in the 1990s, INBIFO researchers published only articles advantageous to industry positions on the consequences of smoke exposure. Unfavourable studies were kept from publication.⁸⁴ In trial testimony, Dr Carchman’s involvement with biological research at INBIFO was discussed, and during his 17 May 1999 testimony in *Butler v. Philip Morris* he reported, “*Philip Morris and INBIFO started their[passive smoking] animal work in about ‘81’*.”⁸⁵

In discussing epidemiologic evidence, the defence witnesses turned to the restrictive causal paradigm proposed by the industry and cited the lack of animal models as evidence against causation. The experts also criticised models that had been developed for their relevance to human exposures. Drs Carchman, Coggins, and Jenkins all cited these issues. For example, Dr Coggins stated: “*Epidemiology on its own cannot prove causation. I don’t think the animal studies on their own can prove causation. With the convergence of data between the two, I believe we need a mechanism before we can use the scientific term cause. The epidemiology on smoking and lung cancer are very variable...But the data from the animal studies are very clear. There are no increases in lung cancer. So we have a dilemma between these two different sources of information.*”¹⁸ Statements by Dr Jenkins attempted to limit utility of the animal studies in support of causation. “*ETS is very complex...what you think you’re exposing*

Table 5 Summary of peer-reviewed meta-analysis publications

Authors	Funding	Quote
Biggerstaff, Tweedie & Mengersen	Three tobacco companies	“Such inhomogeneity is shown to make small, but important, differences in point estimates: the overall excess risk for females is shown to be reduced by perhaps 65%, from 0.12 to 0.04, if Carlin’s model is used rather than the random effects model...”
Fleiss & Gross	Tobacco Institute	“Given the biases that exist in each individual study, the safest conclusion from the present meta-analysis is a negative one: there is no convincing scientific evidence from the epidemiological literature of an association between exposure to ETS and the risk of lung cancer in the U.S.”
Lee	Philip Morris	“Greater progress could, perhaps, be made if meta-analyses were based not on published RRs, but on the raw data from each study. This would enable analytic methods to be standardized and tests of heterogeneity to be improved and extended.”
Tweedie & Mengersen	Not listed	“The real danger with any meta-analysis is the spurious inflation of results due to omission of unpublished negative results. One must include, at least initially, all available studies unless there is a clear and documented reason to omit them, and the analysis above does this.”
Tweedie & Mengersen	Tobacco companies	“From the meta-analysis of studies of lung cancer and exposure to ETS in non-smoking females given here, our conclusion is that, despite a significant observed relative risk associated with overall exposure, there is little increase in relative risk with increasing dose. One explanation that accounts for this somewhat unexpected situation, of an overall observed increased relative risk but little indication of positive dose response, is that some bias may be inflating all of the observed risks.”

the animals to may be considerably different than what you're exposing the animals [sic] to based on the number of all these different interactions that we discussed..."³⁹

Additionally, experts challenged findings of studies conducted by Dr Hanspeter Witschi from University of California, Davis, who studied the carcinogenicity of ETS as it related to the development of lung tumours in A/J mice. Though a target for criticism by the industry experts, Dr Witschi received CIAR funding and published with Dr Coggins.^{86 87} Dr Witschi also worked with Dr Carchman and conducted research at INBIFO. Nevertheless, the defence statements related specifically to Witschi's model and the level of exposure, which was far greater than real world situations.⁸⁸⁻⁹⁰ Dr Jenkins argued that the exposure concentrations in the Witschi animal models failed to represent human exposure. "...One of the Witschi papers, for example, that the concentration of RSP is measured to be 80 — 87 milligrams per cubic meter...That's in many cases 1,000 times higher than most people ever see ETS particulate mater."⁹¹

Dr Coggins challenged the vulnerability of A/J mice and the extreme levels of exposure: "...we used .1, 1, and 10 milligrams of cubic meter[sic]. We think .1 is a high real world estimate. Dr. Witschi...used 87 milligrams of cubic meter[sic]. I think that's getting to be almost as concentrated as mainstream smoke."⁹²

Dr Witschi testified on behalf of the plaintiffs and agreed with the criticisms of exposure and limitations of the conclusions drawn.⁹³⁻⁹⁵ He still maintains that "there are very few—some might say none at all—studies in which it has been unequivocally demonstrated that tobacco smoke can cause lung cancer in experimental animals".⁹⁶

DISCUSSION

The validity of the findings of epidemiological research on the health consequences of passive smoking has been contested vigorously by the tobacco industry. The trial testimony and depositions show a sweeping effort to discredit the findings of epidemiological research generally and to highlight potential methodological issues more specifically. We classified the attack on epidemiological evidence into four strata and found multiple examples of each in the reviewed materials. The overall strategy of discrediting epidemiology mirrored the tactics used decades earlier for active smoking that were intended to maintain controversy on the scientific evidence.

Our findings show that the industry attempted to create a parallel base of published literature supporting claims that the epidemiological findings on secondhand smoke and health reflected bias and not cause. Studies were carried out to strengthen the argument that confounding was responsible for observed associations and that uncontrolled exposure misclassification complicated interpretation of results. Statisticians were supported by the industry to write papers that clouded the interpretation of meta-analyses carried out to pool the evidence from individual studies on second-hand smoke and disease.^{79 81 82} Though not often cited directly within depositions and testimonies by defence witnesses, the statements made by these witnesses and quoted in this review reflect the same general themes as in the industry-supported research and publications.

In building a case for causation, epidemiologists and other health scientists carefully evaluate and synthesise all relevant lines of evidence. Sources of bias are considered carefully as alternatives to causation in producing observed associations. The epidemiological data are interpreted in a context set by relevant biological information. In the face of this well established approach, the tobacco industry attempted to redirect the focus and dialogue related to the epidemiologic evidence of passive smoking. They emphasised potential,

recognised limitations of observational studies, without acknowledging that these potential limitations could be addressed. Additionally, the industry experts attempted to reverse the epidemiologic approach for the synthesis of evidence, by placing bias as a certain alternative to causation and proposing a rigid criterion for identification of mechanisms that might not ever be met. The experts repeatedly posed these arguments, even though their alternative framework was not consistent with epidemiologic theory and practice.

The approach of reviewing, evaluating and synthesising evidence as a basis for making causal claims has proved effective in tobacco control. The review process leading to causal conclusions in these reports reflects the collective effort of a group of experts and not of any particular individual; the process covers arguments that would be raised by critics and of necessity sets them aside in reaching a causal conclusion. The arguments of single, paid witnesses have little credibility when weighed against reports of the Surgeon General, the World Health Organization, the National Research Council and other organisations. In legal settings and other venues where the scientific basis for tobacco control may be questioned, these reports should be the foundation for countering industry strategies. For an example of rebuttal of these tactics in a legal setting, see written trial testimony prepared by one of the authors (JMS) for the lawsuit brought by the US Department of Justice against the tobacco industry (<http://www.usdoj.gov/civil/cases/tobacco2/>).

For tobacco control researchers and practitioners who need to respond to industry criticisms and critics, we have suggested approaches for handling the four major strategies reviewed. With regard to the strategy of being dismissive of epidemiologic research generally, particularly of evidence related to smaller risks on "health effects", the origins of this approach with the tobacco industry and other industries affected by epidemiologic evidence are well documented.^{10 97 98} There is ample countering literature, as well, on the benefits to public health policies based on findings of epidemiological studies.⁹⁹ The persistent claims that confounding explains association becomes empty when it is made in the face of mounting and consistent evidence that has carefully addressed confounding. Certainly, at this time, the evidence is substantial and consistent for the major health effects of second-hand smoke.^{100 101} Given the widespread use of meta-analysis, the claim that it has limitations for application to second-hand smoke has little credibility. With regard to the strategy of questioning the biological plausibility of findings, a "bar" of evidence may be set in terms of mechanistic understanding that cannot be reached. In countering criticisms around biologic plausibility, there is substantial literature on disease pathogenesis in relation to tobacco smoking in general, to second-hand smoke more specifically, and expert reports have repeatedly demonstrated plausibility for causal associations of second-hand smoke with adverse health effects.

Just as the tobacco industry developed a strategy to protect its own interests by labelling the epidemiology as "junk science" or "soft science", with the goal of minimising the impact on public policy and public opinion, these general themes are played out in other venues. Unfortunately, epidemiology has been given this pejorative label and the strategy of using the "junk science" label has been used by other parties with financial interests threatened by epidemiological evidence. Criticisms based on the possibility of uncontrolled confounding and the limited utility of epidemiology for "weak effects" have been made in reference to studies of other environmental agents, including air pollution and radiation. In the example of secondhand smoke, these tactics have not remained tenable over time as the scientific

What this paper adds

The use of the Tobacco Deposition and Trial Testimony Archive (DATTA) database provides a new form of tobacco control research to conduct a qualitative review of depositions and trial testimony to further document the tactics used by the tobacco industry. This review has identified expert witnesses used by the tobacco industry to dispute the epidemiologic findings related to the health consequences of passive smoking. The evidence discusses how the overall strategies used during trials match those used in industry-funded research.

evidence continues to mount. Recent reports from the US Surgeon General and the California Environmental Protection Agency have greatly lengthened the list of diseases caused by involuntary smoking.^{100 101}

Has the industry had success in using these tactics to discredit epidemiologic research? As the first studies were reported linking secondhand smoke to lung cancer and other diseases, alternative explanations to causation were sought by epidemiologists, including many without ties to the tobacco industry. One of the authors of this commentary (JMS) raised methodologic concerns in initial reviews of the evidence.^{102 103} Arguably, the focus on methodologic concerns by industry-funded critics forced a comprehensive explanation of the evidence for misleading flaws so that industry arguments could be set aside. Nonetheless, the industry scientists and consultants persisted in using increasingly predictable but less defensible arguments, as documented in this review. The credibility of their consultants was seriously undermined when connections to the industry were revealed in the industry documents.

In the future, scientists and advocates should be prepared to address these tactics as they are applied to other public health research topics. Applying the lessons learned from the tobacco industry, their scientists, and their consultants will be an additional, yet vital, step in the process of epidemiologic research.

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Authors' affiliations

J A Francis, A K Shea, J M Samet,* Institute for Global Tobacco Control, Johns Hopkins School of Public Health, Baltimore, Maryland, USA

*Also Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

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