It’s what you don’t see that counts: a peek behind the smokescreen

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Methodology Checklist 2: Controlled Trials

SIGN

Study identification *(Include author, title, year of publication, journal title, pages)*

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

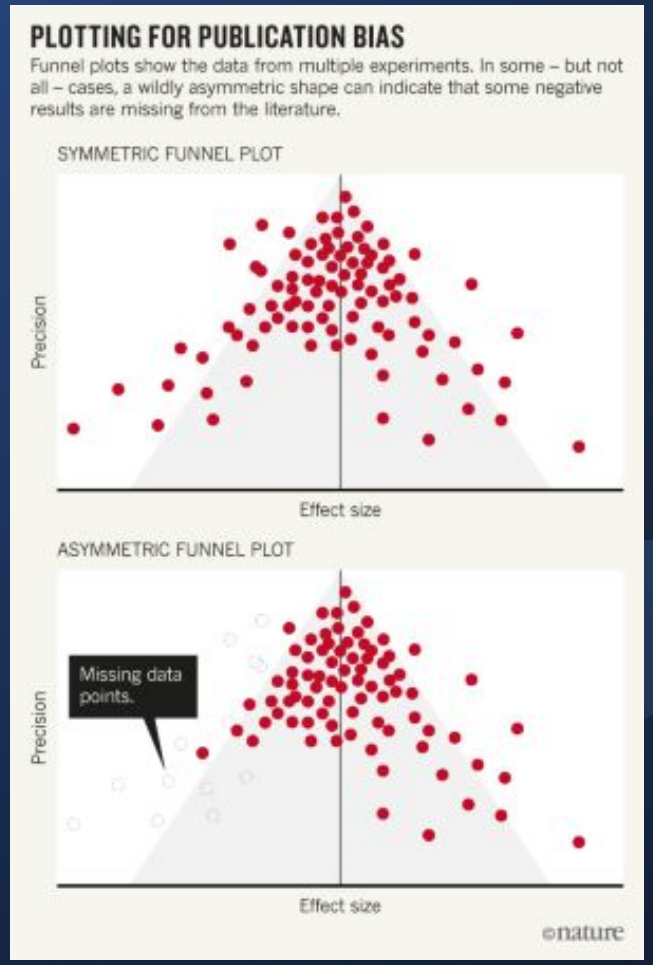
SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study...	*Does this study do it?*
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

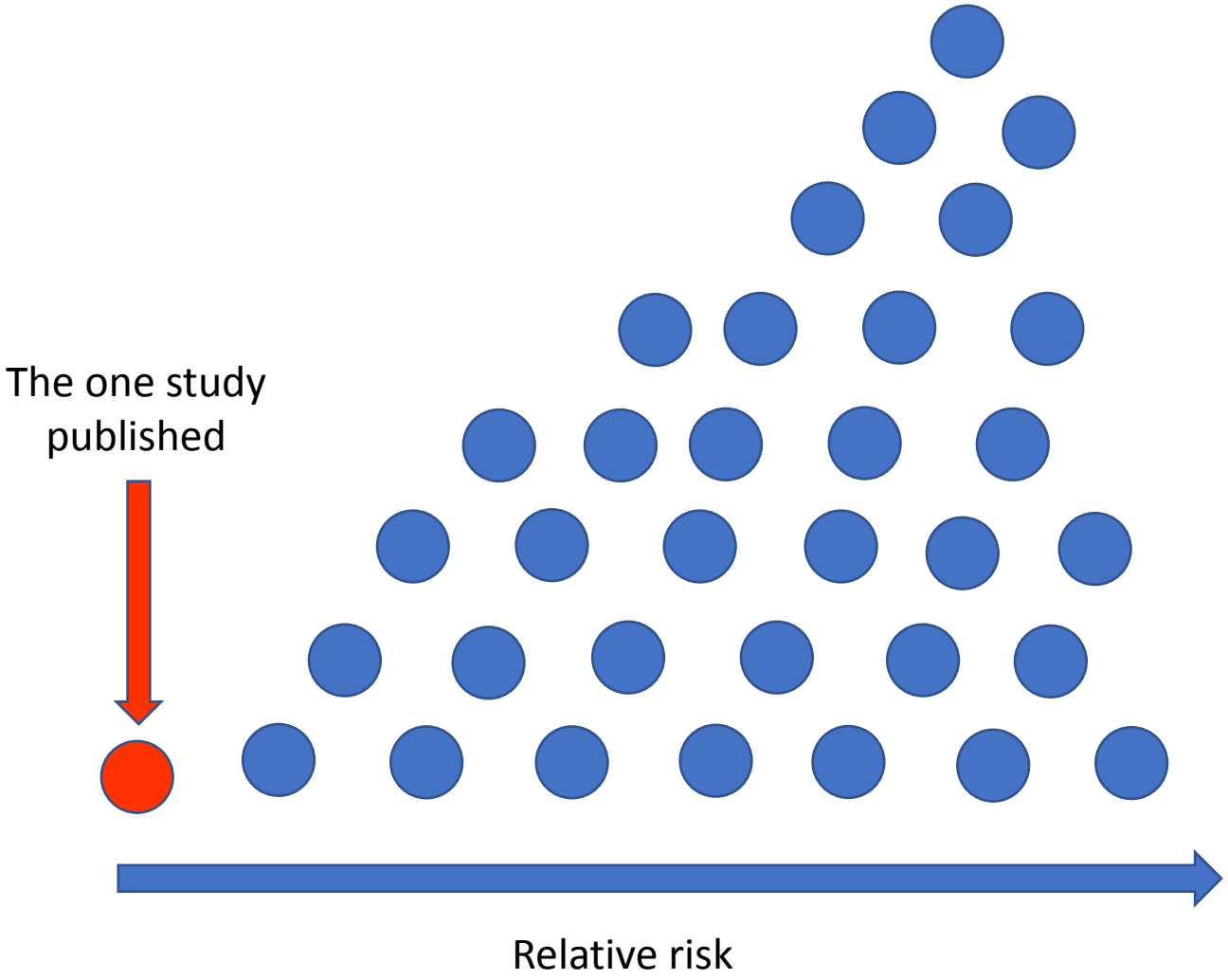
2.1	How well was the study done to minimise bias? *Code as follows:*	High quality (++)☐ Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

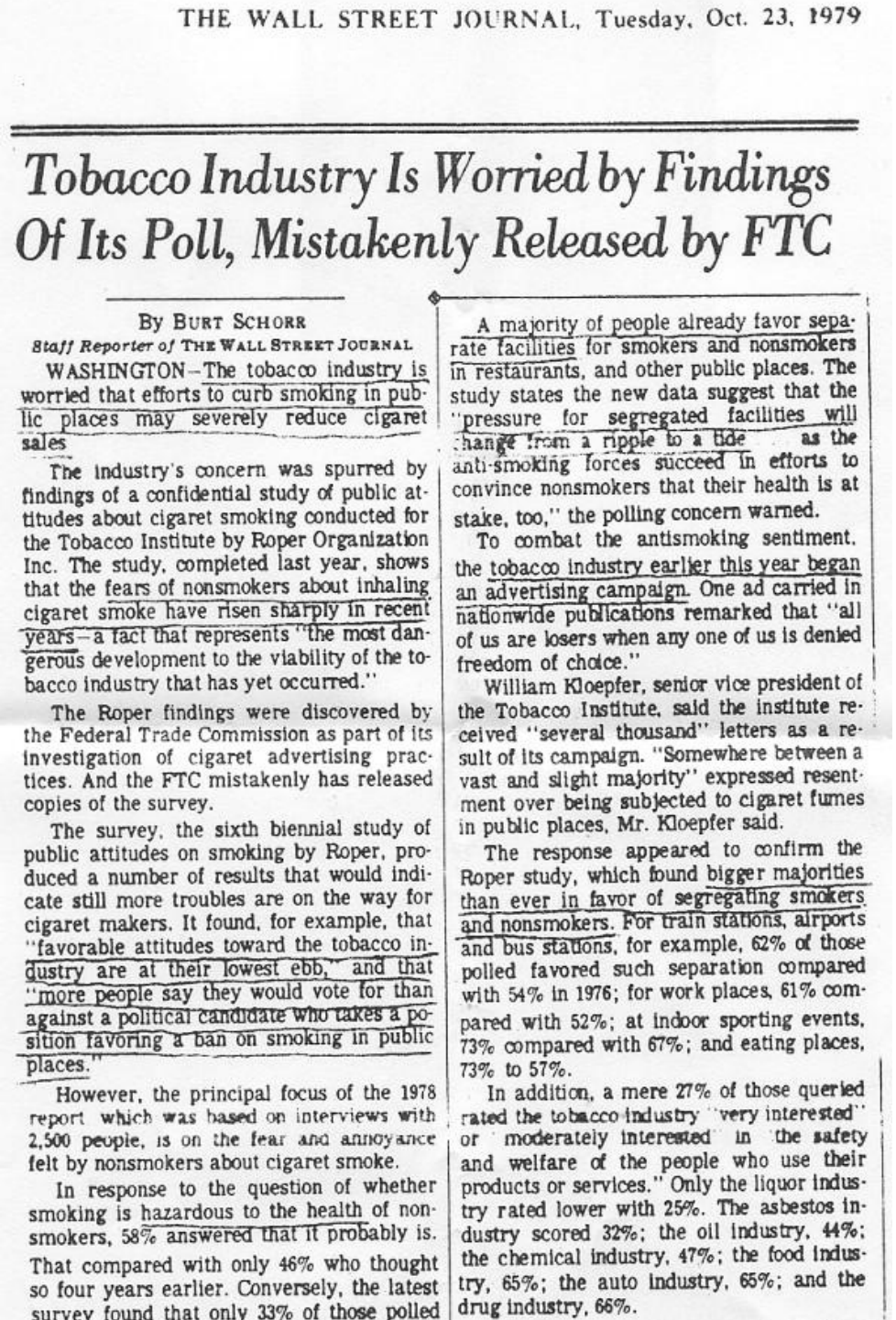
But what about the studies that were not reported?



https://www.nature.com/articles/nature.2017.21728

All studies undertaken





THE WALL STREET JOURNAL, Tuesday, Oct. 23, 1979

Tobacco Industry Is Worried by Findings Of Its Poll, Mistakenly Released by FTC

By Burt Schorr
Staff Reporter of The Wall Street Journal

WASHINGTON—The tobacco industry is worried that efforts to curb smoking in public places may severely reduce cigaret sales.

The industry's concern was spurred by findings of a confidential study of public attitudes about cigaret smoking conducted for the Tobacco Institute by Roper Organization Inc. The study, completed last year, shows that the fears of nonsmokers about inhaling cigaret smoke have risen sharply in recent years—a fact that represents "the most dangerous development to the viability of the tobacco industry that has yet occurred."

The Roper findings were discovered by the Federal Trade Commission as part of its investigation of cigaret advertising practices. And the FTC mistakenly has released copies of the survey.

The survey, the sixth biennial study of public attitudes on smoking by Roper, produced a number of results that would indicate still more troubles are on the way for cigaret makers. It found, for example, that "favorable attitudes toward the tobacco industry are at their lowest ebb," and that "more people say they would vote for than against a political candidate who takes a position favoring a ban on smoking in public places."

However, the principal focus of the 1978 report which was based on interviews with 2,500 people, is on the fear and annoyance felt by nonsmokers about cigaret smoke.

In response to the question of whether smoking is hazardous to the health of nonsmokers, 58% answered that it probably is. That compared with only 46% who thought so four years earlier. Conversely, the latest survey found that only 33% of those polled

A majority of people already favor separate facilities for smokers and nonsmokers in restaurants, and other public places. The study states the new data suggest that the "pressure for segregated facilities will change from a ripple to a tide as the anti-smoking forces succeed in efforts to convince nonsmokers that their health is at stake, too," the polling concern warned.

To combat the antismoking sentiment, the tobacco industry earlier this year began an advertising campaign. One ad carried in nationwide publications remarked that "all of us are losers when any one of us is denied freedom of choice."

William Kloepfer, senior vice president of the Tobacco Institute, said the institute received "several thousand" letters as a result of its campaign. "Somewhere between a vast and slight majority" expressed resentment over being subjected to cigaret fumes in public places, Mr. Kloepfer said.

The response appeared to confirm the Roper study, which found bigger majorities than ever in favor of segregating smokers and nonsmokers. For train stations, airports and bus stations, for example, 62% of those polled favored such separation compared with 54% in 1976; for work places, 61% compared with 52%; at indoor sporting events, 73% compared with 67%; and eating places, 73% to 57%.

In addition, a mere 27% of those queried rated the tobacco industry "very interested" or "moderately interested" in "the safety and welfare of the people who use their products or services." Only the liquor industry rated lower with 25%. The asbestos industry scored 32%; the oil industry, 44%; the chemical industry, 47%; the food industry, 65%; the auto industry, 65%; and the drug industry, 66%.

The background

- Growing evidence of popular demand for smoke-free environments as long ago as 1979
- 27% of Americans believed tobacco industry very or moderately interested in welfare of those who use their products

The official position (I)

- Epidemiological research cannot prove a causal link between exposure to tobacco smoke and disease
- Especially in the case of passive smoking, the “apparently” increased relative risks are too small to provide confidence
  - In parallel, they secretly funded often unsuspecting epidemiologists to agree a code of “Good Epidemiology Practice, which advises discounting RRs less than 2, with the RR typically found in studies of passive smoking about 1.3

The official position (II)

- Even if an effect can be demonstrated, it is most likely to be attributable to confounding, as those who live with smokers differ from those who don’t in many ways (such as diet) and not only in their exposure to smoke
- There is no biological evidence that second hand smoke causes disease

The crux of the matter, in brief …

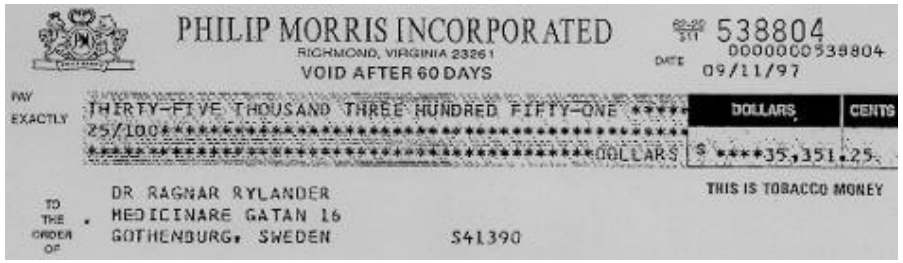
“We within the industry are ignorant of any relationship between smoking and disease. Within our laboratories no work is being conducted on biological systems”.

Dunn, W.L. "the Nicotine Receptor Program". 21 Mar 1980.

How I got involved

To cut a very long story short …

- As a journal editor, I published a paper by a Swedish professor, Ragnar Rylander, on characteristics of women married to smokers and no-smokers – what we now know as confounder studies
- I was told he had undeclared links to Big Tobacco
- He denied it and a long correspondence followed
- Meanwhile he sued two anti-tobacco advocates in Geneva for libel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THIS IS TOBACCO MONEY
TO THE ORDER OF
DR RAGNAR RYLANDER
MEDICINARE GATAN 16
GOTHENBURG, SWEDEN
541390

What did Rylander do?

- Rylander acted as a link between a testing plant, INBIFO, situated in Germany, and Philip Morris' headquarters, in Richmond, Virginia Rylander organised a series of symposia "to convey the message to researchers and to the general public that the available data on the harmful effects of smoke on non-smokers was insufficient and inconclusive, notably in view of other factors susceptible of influencing their health" *(Swiss Court judgement)*
- Rylander worked closely with the Kansas law firm, Shook, Hardy and Bacon, who were at the centre of the campaign to distort the evidence on passive smoking, designing the strategy, commissioning "spoiler" studies and lobbying
- Rylander, on at least one occasion, altered his results after conferring with Philip Morris

Memo from Shook, Hardy and Bacon

“Dr. Rylander prepared a brief memorandum "for internal use only" concerning the workshop. His major point was that he did not feel that the workshop could or would be in a position to give environmental tobacco smoke a "clean bill of health." However, Dr. Rylander did believe that he could bring a healthy scepticism to the conference and some of the claims being made about environmental tobacco smoke.”

Back to INBIFO …

A reminder:

“We within the industry are ignorant of any relationship between smoking and disease. Within our laboratories no work is being conducted on biological systems”.

Dunn, W.L. "the Nicotine Receptor Program". 21 Mar 1980.

In reality …

- In 1968 Helmut Wakeham, PM vice president, expressed concern that the industry was depending on its *“technical intelligence system”* to alert them to scientific developments
- The information was often available only after publication
- Much of the research was from studies *“oriented to seeking out and highlighting the negatives associated with tobacco smoke”*
- There was a need to *“obtain our own facts and data in biological systems, in order to avoid being surprised by information from outside sources and in order to interpret and understand the results of such studies”*

Making it happen

- PM was not the first – American Tobacco had already taken its biological research and *“relocated [it] under conditions of extreme secrecy … to new research facilities”*
- However the approach was controversial within the company - Chairman and chief executive Joseph F Cullman had *“serious reservations about the wisdom of embarking upon this program at this time”*
- He was eventually convinced and agreed that research could be undertaken *“on a contractual basis in Europe … presents an opportunity that is relatively lacking in risk and unattractive repercussions in this country”*

An opportunity presents itself

- In 1970, the Institut für Industrielle und Biologische Forschung GmbH (INBIFO) came on the market
- Wakeham advocated the purchase of INBIFO by Philip Morris as *"this is a locale where we might do some of the things which we are reluctant to do in this country"*
- *"Let's face it. We are interested in evidence which we believe denies the allegation that cigaret (sic) smoking causes disease"*

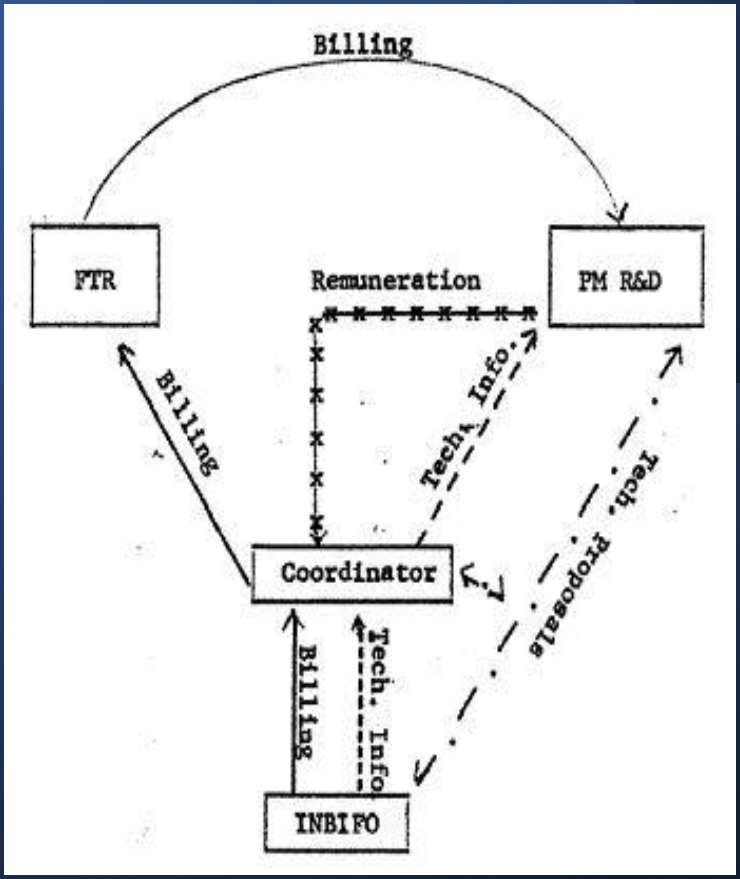
The options

- Conduct research for other causes of smoking-related diseases, to get the industry *“off the hook”*, although *“prospects for a positive benefit are small”*.
- Establish *“expert scientific witnesses who will testify on behalf of the Industry”*, although it may not be long before such witnesses were tainted by association with the industry.
- Undertake research to discover information of direct use to the industry on biological, psychosocial and epidemiological aspects of smoking.

Keeping it at arm's length

- INBIFO was purchased on behalf of Fabrique de Tabac Réunies, based in Neuchâtel, Switzerland
- *"In this way our involvement would not be unduly exposed"*

The matrix of relationships



- Rylander, as co-ordinator, would *"officially … carried on the books as a consultant to FTR [a Philip Morris subsidiary] and would be paid by FTR"* (emphasis added).
- There was to be no formal connection between Philip Morris and INBIFO
- However any proposals for studies would be authorised by Philip Morris, with the coordinator simply being informed of the decision.

A culture of secrecy

- On an analysis of a new flavour formula in 1976: *“We may want to maintain confidentiality over the results; therefore, thought should be given to the use of INBIFO”*
- *"We are still anxious to keep confidential the fact that INBIFO has done its own glycerol inhalation study."*

An insider's view

"I subsequently found out (by asking around) that hardly anyone [at Philip Morris] knew anything about INBIFO … I also remember hearing that on occasion, some of the results and/or initial observations from some of Dr Osdene's programs were being communicated verbally, rather than in writing. … All in all, it seemed as if there was an 'inner company' within Philip Morris that conducted at least some of its investigations 'behind the scenes' on a strict 'need-to-know' basis. Interestingly enough, many (if not all) of these activities appeared to be related, in one way or another, to these sensitive topics of 'smoking and health'".

Testimony of Ian Uydess, a former Philip Morris employer, 1996

Maintaining the secrecy (I)

- When a researcher in Philip Morris' Swiss research centre suggested that samples might be send directly to INBIFO he was reprimanded: *"This suggested procedure is in direct conflict with our communications from the New York Office. We have gone to great pains to eliminate any written contact with INBIFO, and I would like to maintain this structure. Therefore I am advising … to continue sending samples to Neuchatel for transhipment to INBIFO. If this procedure is unacceptable to you, perhaps we should consider a "dummy" mailing address in Köln for the receipt of samples. The written analytical data will still have to be routed through FTR if we are to avoid direct contact with INBIFO and Philip Morris USA."*
- *The executive then* requested the researcher to retrieve all copies of his original letter.

Maintaining the secrecy (II)

- Advice from Tom Osdene on communicating with INBIFO: *“OK to phone & telex (these will be destroyed)”*, and *“If <u>important</u> letters or documents have to be sent please send home – I will act on them & destroy”*
- Letter from INBIFO to Shook, Hardy & Bacon - *"Except for one brief presentation to the ETSAG [Tobacco Industry Environmental Tobacco Smoke Advisory Group] on one of the INBIFO experiments no one knows anything about our SS [sidestream] work, particularly within PM."*

So what were they doing?

- Over 800 studies on sidestream smoke between 1981 and 1989
- Between 1972 and 1989, 53 publications from INBIFO
- 16% mention tobacco and related terms, even though over 95% of its work was for PM or FTR
- Between 1990 and 1998, 63% of 76 publications concern tobacco
- In 1990, PM were advised that work of INBIFO could no longer be assumed to be safe from disclosure
- At the same time a precautionary review of documents held was undertaken

What did they publish

- Research on possible other causes of lung cancer – the confounder studies – such as the role of green tea
- Research to cast doubt on value of cotinine as a marker of exposure to environmental tobacco smoke
- Research showing that cigarette additives are harmless
- Since 1998, a few papers suggesting that tobacco may indeed be harmful – an attempt to restore credibility?

What they didn’t publish

- In the 1980s there were over 100 animal studies on effects of sidestream smoke
- *"All rats showed general signs of exhaustion after the end of the daily exposure. In contrast to the rats of the mainstream group, which recovered by the next morning, the rats of the sidestream groups continued to show shaggy fur and some pronounced respiratory symptoms characterized by whistling and rattling sounds."*
- *"If one extrapolates from the experience of previous mainstream inhalation studies, the mainstream TPM [total particulate matter] concentration of this study would have to be increased by a factor of 3 to produce similar strong reactions than seen with sidestream exposure in this study."*
- *"Additionally to the changes, seen with mainstream, sidestream - puffed or nonpuffed alike - caused more severe atrophic and necrotic leasons of the olfactory epithelium and frequent squamous cell metaplasia in the ciliated epithelium of the nasal cavity."*

More evidence that sidestream smoke is more dangerous than mainstream

- *"Sidestream smoke of the cigarette type 2R1 showed a higher toxicity in terms of body weight development, food consumptions, rectal temperature and respiratory frequency than mainstream smoke of equal TPM concentration. To reach the same effect on the mentioned bioassays with mainstream and sidestream smoke, the mainstream TPM-dose must be 2 to 4-fold higher than the sidestream TPM-dose."*

So what did Rylander think?

- *"The histology demonstrates more advanced lesions in the nasal epithelium and hyper and metaplasia in areas which are not affected by main stream smoke. The extent of cornification observed in these animals has never been seen before."*

(letter to Tom Osdene)

But it is not enough to know …

- The research conducted by INBIFO provided a means of identifying studies that could be commissioned to others to provide the desired results:
- *“The result of such work has enabled us to provide accurate input … as to what could be expected to be seen in the Bruene experiment and led us to recommend that he support its conduct by the VdC [Verband der Cigarettenindustrie – German Cigarette Manufacturers Association]*

Summary

- By the late 1960s, the tobacco industry realised it needed a capacity to conduct biological research on health effects of tobacco
- Conducting the research in the US was too dangerous
- It had to create a complex, arm's length set of relationships to keep its work secret, even within the company
- Communication was via a Swedish public health professor who maintained an image of independence
- It's not just the research you can see, it's what you can't see
- And anyone who suggests that you can assess industry-funded studies just on the basis of the science contained within them is naive

The final verdict!

GENÈVE TG 16/12/03 23

La crédibilité du professeur Rylander part en fumée

«Genève a bien été la plateforme d'une fraude», explique la Cour. Victoire des antitabagistes.

CATHERINE FOCAS

Les deux antitabagistes genevois, Pascal Diethelm et Jean-Charles Rielle, ont été acquittés, hier, par la Chambre pénale de la Cour de justice. Après de multiples recours, cette instance a considéré que les propos tenus par les deux hommes lors d'une conférence de presse en 2001 n'étaient ni exagérés ni diffamatoires à l'égard du scientifique suédois Ragnar Rylander. «Genève a bien été la plateforme d'une fraude scientifique sans précédent, dit l'arrêt, dans la mesure où Ragnar Rylander a agi en sa qualité de professeur associé de l'Université, profitant de son rayonnement et n'hésitant pas à mettre la science au service de l'argent, au mépris de la mission confiée à cet établissement de droit public.»

En 2001, Pascal Diethelm et Jean-Charles Rielle avaient révélé publiquement les liens entre le médecin environnementaliste suédois et le cigarettier Philip Morris, ils avaient jeté la suspicion sur ses travaux qui tendaient à démontrer que le tabagisme passif n'était pas dangereux pour la santé, notamment pour celle des enfants. L'arrêt est très sévère à l'égard du scientifique de Göteborg: «Les éléments mis en évidence (...) amènent la Chambre pénale à admettre que les appelants n'ont pas exagéré en utilisant le terme de «fraude scientifique» pour qualifier ce double rôle de professeur dans le domaine de la médecine environnementale et de chercheur indépendant que Ragnar Rylander s'est attribué, d'une part, de collaborateur au service d'une industrie qui s'est toujours placée à l'opposé de la santé publique, d'autre part.»

Les juges ajoutent qu'il s'agit bien d'une tromperie «sans précédent» puisqu'elle s'est étendue sur une trentaine d'années et qu'elle a été entretenue «au prix de mensonges».

Désinformation scientifique

La lecture de cet arrêt est passionnante. Il décrit comment un scientifique de renom, élégant et au-dessus de tout soupçon, se laisse peu à peu corrompre. Comment, par amour de l'argent, il se met au service de la désinformation scientifique, par petites touches, discrètes mais redoutables. Ainsi, dès 1972, Ragnar Rylander travaillait pour le laboratoire INBIFO à Cologne. Ce laboratoire était en fait, une des officines des cigarettiers, mais cela devait rester top secret tout comme les résultats des expériences qui y étaient menées.

En 1973, le scientifique suédois organise un symposium dont le but est d'obtenir un document final permettant de calmer «une certaine hystérie» concernant les effets du tabagisme passif. La préoccupation principale est d'influencer l'évolution de la législation des gouvernements voulant instaurer des restrictions pour les fumeurs. Et de faire croire que le risque de développer une affection pulmonaire chronique n'est en aucune façon lié à l'exposition au tabac. Un deuxième symposium du même genre est organisé en 1983 à Genève cette fois.

En 1991, le scientifique suédois démontrait (après avoir corrigé la banque de données!) que les maladies respiratoires des enfants étaient sans rapport avec la fumée passive. Selon le chercheur, celles-ci étaient induites par la consommation d'œufs, de fromage et de produits laitiers...

La Cour de justice relève que «l'existence d'un lien direct entre la fumée passive et le cancer était connue par Philip Morris depuis 1965 en tout cas. Nonobstant ce lien, le cigarettier avait refusé d'en admettre la réalité jusqu'en l'an 2000. Le professeur Ragnar Rylander qui était au courant de cette réalité avait participé à ce déni.»

Il faut dire aussi qu'il recevait entre 120 000 et 140 000 dollars par année.

Lire l'éditorial en page 4

INDUSTRIE DU TABAC

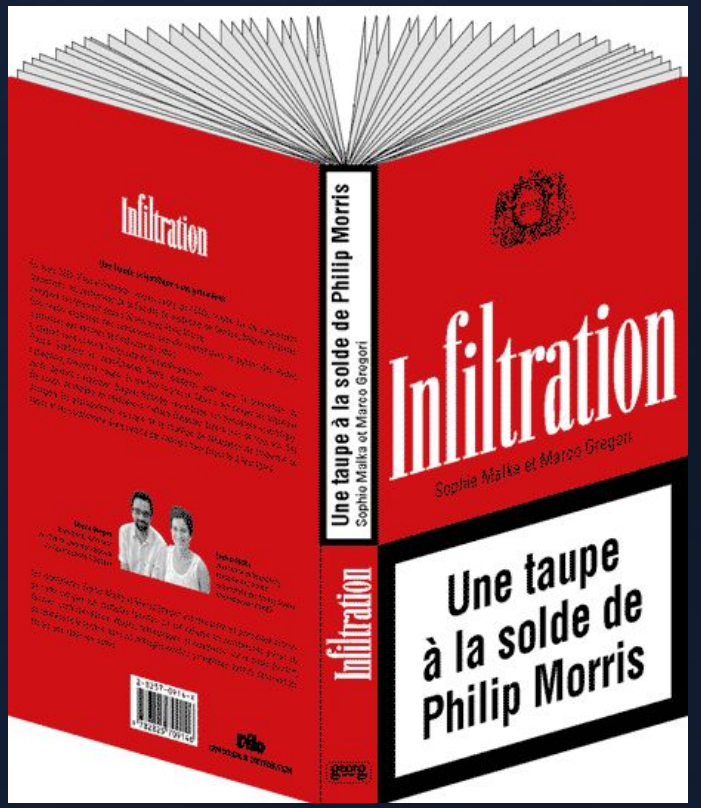
TW 16/12/03

David bat Goliath

■ Après deux ans et demi de procédure, l'affaire Rylander, du nom de ce professeur suédois accusé de fraude scientifique pour le compte de l'industrie du tabac, a probablement trouvé son épilogue à Genève. La Cour de justice genevoise a en effet acquitté hier deux responsables de la lutte antitabac poursuivis en justice pour diffamation. Le professeur devra quant à lui s'acquitter des frais de procédure, soit un peu plus de 10 000 francs.

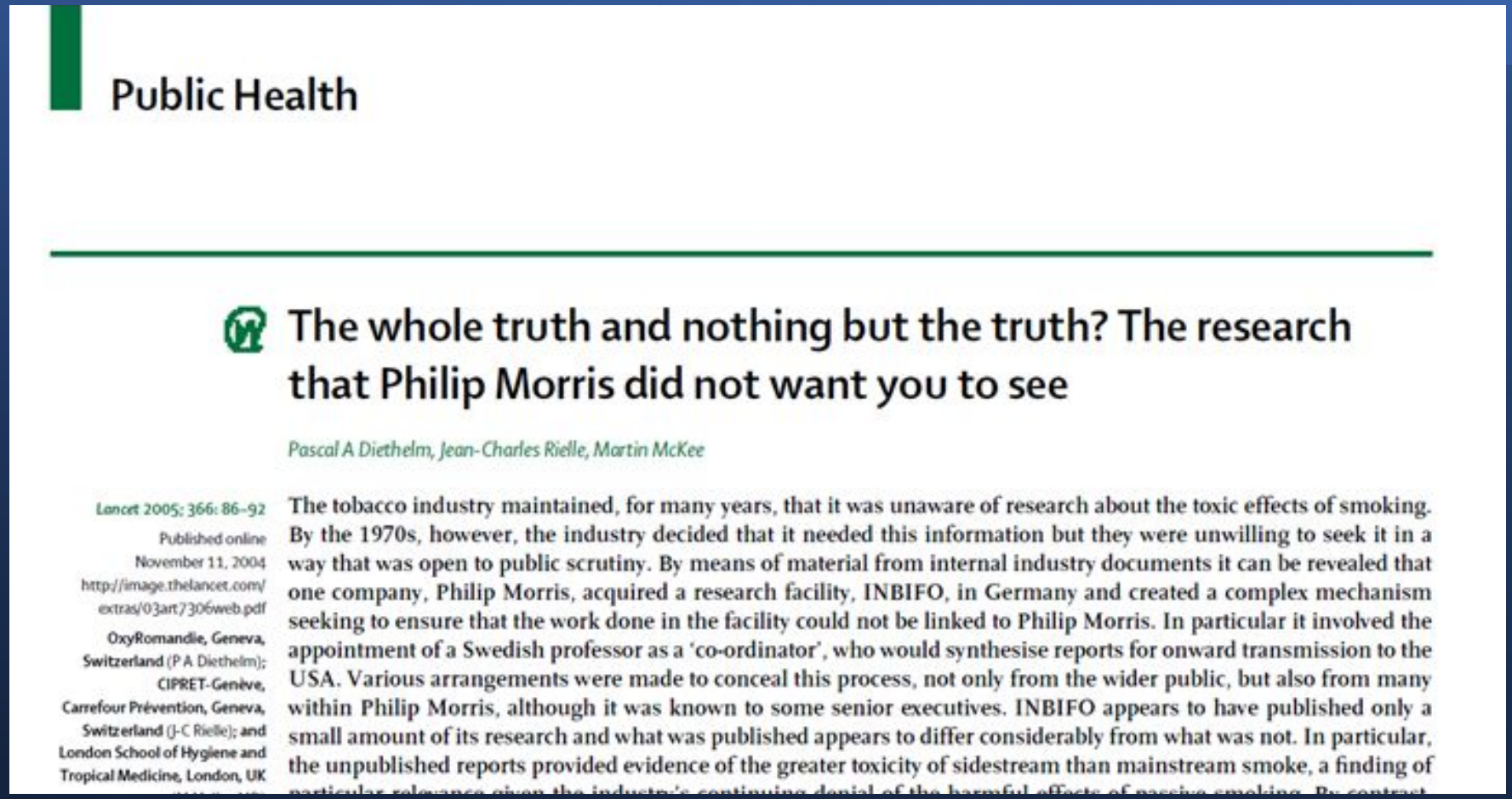
«Cette décision est une importante victoire pour la santé publique et pour l'intégrité de la recherche scientifique, en Suisse et dans le monde», se réjouissent le Dr Jean-Charles Rielle, attaché à la Direction du Service genevois de santé de la jeunesse et responsable du CIPRET, et Pascal Diethelm, président d'OxyGenève. En conférence de presse en mars 2001, les deux anti-tabagistes avaient dénoncé les liens unissant Ragnar Rylander, professeur associé durant près de 30 ans à l'Université de Genève, à Philipp Morris. Ils avaient présenté le Suédois comme l'auteur d'une *«fraude scientifique sans précédent»* sur les dangers de la fumée passive.

AP



With thanks to Pascal Diethelm and Jean-Charles Rielle

Further reading



Public Health

The whole truth and nothing but the truth? The research that Philip Morris did not want you to see

Pascal A Diethelm, Jean-Charles Rielle, Martin McKee

Lancet 2005; 366: 86–92
Published online November 11, 2004
http://image.thelancet.com/extras/03art7306web.pdf

OxyRomandie, Geneva, Switzerland (P A Diethelm); CIPRET-Genève, Carrefour Prévention, Geneva, Switzerland (J-C Rielle); and London School of Hygiene and Tropical Medicine, London, UK

The tobacco industry maintained, for many years, that it was unaware of research about the toxic effects of smoking. By the 1970s, however, the industry decided that it needed this information but they were unwilling to seek it in a way that was open to public scrutiny. By means of material from internal industry documents it can be revealed that one company, Philip Morris, acquired a research facility, INBIFO, in Germany and created a complex mechanism seeking to ensure that the work done in the facility could not be linked to Philip Morris. In particular it involved the appointment of a Swedish professor as a 'co-ordinator', who would synthesise reports for onward transmission to the USA. Various arrangements were made to conceal this process, not only from the wider public, but also from many within Philip Morris, although it was known to some senior executives. INBIFO appears to have published only a small amount of its research and what was published appears to differ considerably from what was not. In particular, the unpublished reports provided evidence of the greater toxicity of sidestream than mainstream smoke, a finding of