

The p53 tumour suppressor gene and the tobacco industry: research, debate, and conflict of interest



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Mutations in the p53 tumour suppressor gene lead to uncontrolled cell division and are found in over 50% of all human tumours, including 60% of lung cancers. Research published in 1996 by Denissenko and colleagues demonstrated patterned in-vitro mutagenic effects on p53 of benzo[a]pyrene, a carcinogen present in tobacco smoke. We investigated the tobacco industry's response to p53 research linking smoking to cancer. We searched online tobacco document archives, including the Legacy Tobacco Documents Library and Tobacco Documents Online, and archives maintained by tobacco companies such as Philip Morris and R J Reynolds. Documents were also obtained from the British American Tobacco Company depository in Guildford, UK. Informal correspondence was carried out with scientists, lawyers, and tobacco control experts in the USA and Europe. We found that executives and scientists at the highest levels of the tobacco industry anticipated and carefully monitored p53 research. The tobacco industry's own scientists conducted research which appeared to cast doubt on the link between smoking and p53 mutations. Researchers and a journal editor with tobacco industry ties participated in the publication of this research in a peer-reviewed journal without clear disclosure of their tobacco industry links. Tobacco industry responses to research linking smoking to carcinogenic p53 mutations mirror prior industry efforts to challenge the science linking smoking and lung cancer. The extent of tobacco industry involvement in p53 research and the potential conflict of interest discussed here demonstrate the need for consistent standards for the disclosure and evaluation of such potential conflicts in biomedical research.

Introduction

Mutations in the p53 tumour suppressor gene are found in more than 50% of all human tumours,¹ including 60% of lung cancers.² In the normal cell, p53 defends against uncontrolled proliferation by causing G1 cell-cycle arrest and apoptosis (cell suicide) in response to DNA damage by radiation or mutagenic chemicals. p53 mutations contribute to tumour formation as they contribute to uncontrolled cell division regardless of DNA damage.

Because of tobacco use, lung cancer is the leading cause of cancer death in developed nations.³ Benzo[a]pyrene, a potent carcinogen, was identified in cigarette smoke by Brown and Williamson Tobacco Company scientists as early as 1952.⁴ In the 1990s, in-vitro experiments⁵ and human molecular epidemiology studies⁶ demonstrated patterned damage to the p53 gene resulting from exposure to benzo[a]pyrene's mutagenically active metabolite (+/-) anti-7 β ,8 α dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE). In 1996, Denissenko and colleagues⁵ at the Beckman Research Institute in Duarte, CA, USA published a landmark analysis of BPDE's interaction with p53 in the journal *Science*. Analysing in-vitro culture cells and bronchial epithelial cells exposed to BPDE, Denissenko and colleagues identified a pattern of adducts along the p53 gene that correlated strongly with database analyses of p53 mutations found in actual human lung tumours available at the time.⁷ This finding provided strong molecular evidence of the direct carcinogenic effect of a tobacco smoke constituent, findings that were verified by subsequent epidemiological analyses of p53 mutation databases.⁶

This paper describes the tobacco industry's response to Denissenko and colleagues' findings and subsequent research linking tobacco smoke exposure to patterned

p53 mutations. Previously confidential tobacco industry documents demonstrate that prior to 1996 several tobacco companies supported research projects investigating mechanisms of p53 mutagenesis. Following the publication of Denissenko and colleagues' findings, tobacco companies supported scientific studies which appeared to cast doubt on the link between p53 damage and BDPE in tobacco smoke. In one case, a journal editor with longstanding, undisclosed ties to the tobacco industry proposed such a research project to a tobacco company prior to the publication of similar studies in his journal. The publication of this research in the journal *Mutagenesis* occurred without clear disclosure of tobacco industry connections on the part of the authors, and without any disclosure of tobacco industry ties on the part of the editor.

Document search

We examined tobacco industry documents made public as a result of litigation against the tobacco industry in the USA. Between September, 2002, and November, 2003, we searched tobacco industry document internet sites: University of California San Francisco Legacy Tobacco Documents Library (<http://legacy.library.ucsf.edu>); British American Tobacco (BAT) collection (<http://www.library.ucsf.edu/tobacco/batco>); archives maintained by R J Reynolds (RJR; <http://www.rjrtdocs.com>) and Philip Morris (PM; <http://www.pmdocs.com>); and Tobacco Documents Online (<http://www.tobaccodocuments.org>). Searches began with general terms such as "p53" and "mutagenesis," then were narrowed using Boolean operators such as "AND" and "OR" to include names, locations, dates, and reference (Bates) numbers. For example, using the

Legacy Tobacco Documents Library, the search terms “p53,” “mutagenesis”, and “tumor suppressor” yielded 3308 documents, 2276 documents, and 875 documents, respectively. A search for “p53 AND mutation” yielded 410 documents.

An additional 15 000 pages were obtained in hard copy format from the British American Tobacco Document Depository in Guildford, UK, by arranging for a research assistant to search the depository for files indexed with terms including “p53” and the names of people and journals identified through other internet searches. In September, 2004, many of these documents were made available on the internet at <http://bat.library.ucsf.edu>.

Of the documents reviewed in hard copy and electronic format, 43 were selected for use in this report on the basis of relevance. Additional information concerning the context of the events described in the tobacco documents and the identities of figures named in the documents were obtained using Lexis-Nexis Academic Universe (<http://www.lexis-nexis.com>), MEDLINE, and general internet searches (<http://www.google.com>). Informal e-mail and print correspondence was carried out between May, 2001, and March, 2003, with individuals involved in events described in the documents to clarify the context and sequence of the events described. A number of print and e-mail communications concerning these events were made available to us by Pierre Hainaut.

Background: industry research before 1996

BAT established the Scientific Research Group (SRG) in 1986, “to coordinate and initiate BAT’s knowledge and research . . . on ‘the effects of smoking on the smoker’” through funding and monitoring of external research.⁸ An anonymous 1993 BAT memo lists a number of external contracts, many of which were granted through the SRG,⁹ including one project regarding *p53* and cancer mechanisms. This memo suggests that BAT did not require disclosure of the source of project funding when the results were published:

- “1. We are also making contributions to industry funded research in a number of countries . . .
2. The information on the research organizations supported by BAT should be regard as confidential.
3. In all cases where research is supported by BAT, research workers are free to publish their work without further reference to BAT.”¹⁰

We found evidence that British American Tobacco (BAT) monitored work on *p53* at the highest corporate levels from the late 1980s. In 1993, Richard Thornton, BAT Smoking Issues manager, wrote to then-BAT chairman Barry Bramley, regarding BAT-funded research on *p53*:

“*BAT and p53*
More papers are currently published on *p53* than any other topic on cancer research . . . The SRG identified *p53* as an important area some four years ago and the

SRG currently supports two research projects relating to *p53*. Through one connection in particular we are often aware of work before it is published

p53 and Litigation

. . . Attempts to implicate tobacco by analysis of mutational spectra in *p53* isolated from lung or other cancers may be foreseen.”¹¹

Our search of the documents does not indicate the identity of “the connection” by which the SRG received work before it was published.

The research projects on *p53* mutations supported by the SRG included a grant to researchers at the Marie Curie Institute in Oxted, UK, a part of the UK cancer charity Marie Curie Cancer Care. According to a 1991 memo written by Thornton, “BAT have been supporting a basic research programme involving *p53* at the Marie Curie Research Institute since 1987” that BAT noted as being “considered to have ‘international standing’”.¹² The BAT-funded programme was overseen by Graham Currie, former director of the Marie Curie Institute, and John Jenkins, then a researcher at the Institute. Currie and Jenkins were at the time co-editors of the peer-reviewed journal *Oncogene*, of which Jenkins remained co-editor as of March, 2004.¹³ During the 1980s and 1990s, they published widely on the molecular mechanisms underlying *p53*’s regulation of the cell cycle. This research made no specific reference to tobacco (and was neither favourable nor unfavourable to the tobacco industry).^{14–16} A 1993 SRG report states that “Dr. G. Currie” project had received £240 000 over eight years through 1993 for a project on “*p53* and lung cancer” and “the importance of *p53* to cell division”.⁹

SRG also hired external consultants to analyse trends in *p53* carcinogenesis research, report new findings, and evaluate grant proposals. One of them, Francis Roe, received £8000 from BAT in 1993.¹⁷ In that year, Roe gave a presentation to the BAT SRG, stating:

“on-going research on oncogenes and gene-interventions might at any time lead either to solutions or to yet further problems for the Industry. For this reason it has been very wise for BAT to support the research of Dr. Jenkins and others at the Marie Curie Research Institute on *p53* and other proto-oncogenes. Through this support the Company not only gets an early insight into the results of research on *p53* but maintain access to expertise on oncogenes generally. The ready availability of this expertise might suddenly at any time be found to be of crucial importance.”¹⁸

Beyond BAT’s *p53* research programme, there is evidence that some other tobacco companies and industry groups monitored developments in *p53* research and funded projects examining *p53* in carcinogenesis. Anthony Tricker, a senior scientific adviser to PM who reported directly to Cathy Ellis, PM Worldwide Scientific Affairs and Director of Research at Philip Morris USA in 1994,¹⁹ attended and provided PM with a

report regarding a conference on *p53* and molecular carcinogenesis in 1998.²⁰ RJR and the Council for Tobacco Research contracted with independent laboratories and university-based researchers to do basic research related to *p53*.^{21,22}

Tobacco industry responses to in-vitro research linking *p53*, smoking, and cancer

In October, 1996, Mikhail Denissenko and colleagues⁵ at the Beckman Cancer Research Institute in Duarte, CA, published the results of their in-vitro analysis of the interaction of BPDE with *p53* in the journal *Science*. Application of BPDE to HeLa cells, a standard in-vitro culture cell, and bronchial epithelial cells resulted in strong and selective adduct formation along the *p53* gene, occurring with greatest frequency at codons 157, 248, and 273. Additionally, the authors found that “the majority of lung cancer mutations at these three codon positions are G [guanine] to T [thymidine] transversions”. As shown by the analyses of *p53* mutations found in actual human lung tumours available at the time,⁷ these three codons were common sites of mutation in the *p53* gene in lung cancer. They concluded that “our study thus provides a direct link between a defined cigarette smoke carcinogen and human cancer mutations”.⁵

The initial public responses of tobacco companies such as PM, BAT, and RJR downplayed the mechanistic significance of Denissenko and colleagues’ findings (panel 1) in their statements to investors, analysts, and journalists. These statements mirror tobacco industry arguments first made in 1954, that the precise mechanisms by which smoking might cause cancer remain unknown.⁴

Internally, tobacco companies reviewed the scientific and litigation implications of Denissenko’s work and planned a number of new research projects in response. A technical review of the Denissenko paper dated Oct 18, 1996, was written for PM by Thomas Mueller, a scientist at the Institut für Biologische Forschung (INBIFO) a German laboratory purchased by PM in 1970 “to do some of the things which we are reluctant to do in this country [USA]” through a “first-class self-supporting research facility”.^{26,27} He states that Denissenko’s work “presents solid evidence . . . [and] reveals, in fact for the first time, the coincidence of mutational hot spots described in epidemiological studies and adduct hot spots and suggests the BaP metabolites may be involved in this process”.^{28,29} A 1996 review of Denissenko and colleagues’ report from the office of Cathy Ellis, director of research at PM USA, proposes that PM “support additional research elsewhere” in an attempt to further define the mechanism of *p53* damage by BPDE, investigate the feasibility of screening individuals for susceptibility to *p53* damage, and research possibilities for product modification by PM.³⁰ A separate 1996 PM review notes a number of methodological shortcomings in the study, but states that:

Panel 1: Tobacco industry’s rhetoric related to research on smoking and health

1954: “A frank statement to cigarette smokers”⁴

1. That medical research of recent years indicates many possible causes of lung cancer
2. That there is no agreement among the authorities what the cause is
3. That there is no proof that cigarette smoking is one of the causes
4. That statistics linking cigarette smoking with the disease could apply with equal force to any one of the many other aspects of modern life . . .”

1996: Public statement by Philip Morris (Oct 18)²³

“The research is extremely interesting and merits careful review . . . We look forward to pursuing this and other research in an attempt to learn more about what mechanisms may be at work and what can be done about it . . . The research reported today and the media attention being given to it are consistent with our long-held position that the mechanism by which a cell becomes cancerous is a complex process not yet explained”

1996: Martin Broughton, chief executive of BAT Industries, speaking to investors, analysts, and journalists (Oct 30)²⁴

“There is still a lack of understanding of the mechanisms of diseases attributed to smoking . . . The importance of this *Science Magazine* study may lie, not least, in the recognition that there are important missing links in the understanding of causation . . . It may lead to further research . . . into the complex process by which a cell becomes cancerous. A process we and others have spent millions in trying to understand for many years now.”

1996: Public statement by RJ Reynolds tobacco company (Oct 17)²⁵

“That BaP will cause a mutation has been known for a long time . . . The authors themselves describe these findings as a coincidence. The press release’s conclusion that these [the authors’] findings are the key to lung cancer is an overstatement”

“In spite of these limitations, were [sic] involved in the following efforts which address and evaluate the claims of this study from a number of different perspectives:

First, we have had and will continue to have discussions with key experts on the technical merit and significance of this work.

Second, carefully designed and controlled scientific studies will be performed to investigate the claims of the paper and continue to investigate the formation and reduction of B(a)P in cigarette smoke

Third, product development efforts will continue to pursue commercially viable methods of reducing B(a)P in cigarette smoke.”³¹

A number of these proposed projects were “established at INBIFO”, including genetic sequence

analysis of *p53* mutational spectra in human and animal tumours “to assess the site and type of mutations”.³²

David N Cooper also undertook a critical review of the Denissenko paper. Cooper of the University College of Wales in Cardiff appears in the records of BAT’s SRG beginning in 1991, when he made a presentation on new experimental techniques in molecular genetics.³³ A 1991 SRG memo written by R E Thornton emphasises the applicability of Cooper’s work to *p53* research:

“Dr. Cooper’s hypothesis was likely to apply to disease for which environmental agents had been invoked e.g. lung cancer. Given that mutations in *p53* also appear to follow a pattern, at least in some cancers, it would be interesting to compare the patterns of mutation in some detail . . . Dr. Cooper indicated a willingness to have an on-going dialogue with BAT and I believe that this, and the above, are additional reasons for supporting him.”³⁴

Further, a 1993 SRG report notes the potential applicability of Cooper’s work to the study of “spontaneously occurring genetic mutations to cancer”,³⁵ and the 1993 budget for SRG lists Cooper as expected to receive £25 000 for a report on “mutations and thrombotic disease”.³⁶ We do not know if Cooper actually produced the report.

In July, 1998, Cooper, writing with Michael Krawczak, published a critique of Denissenko and colleagues’ report in *Mutagenesis* arguing that Denissenko’s review of *p53* mutations in databases of actual lung tumours lacked sufficient non-smoking controls, rendering their data “unsubstantiated conjectures”.³⁷ Based on an analysis of the *p53* mutation databases used by Denissenko, Krawczak, and Cooper conclude that Denissenko’s results are “insufficient in general to prove that the *p53* mutations associated with lung cancer are anything other than predominantly endogenous in origin”.³⁷ There is no evidence to suggest that either Cooper or Krawczak received tobacco industry funding for this research. No funding source or competing interests for the authors were reported.³⁷

Tobacco industry response to epidemiological evidence linking *p53*, smoking, and cancer

In a study published in July, 1998, in *Environmental Health Perspectives*, Tina Hernandez-Boussard and Pierre Hainaut⁶ of the International Agency for Research on Cancer (IARC), a branch of WHO in Lyon, France, analysed 876 *p53* mutations from human lung tumours using an online database maintained at IARC. They found a high frequency of mutations at codons 157, 248, and 273, confirming Denissenko and colleagues’ in-vitro findings. Hernandez-Boussard and Hainaut also found a higher frequency of guanine (G) to thymidine (T) transversions among smoking-associated lung tumours than lung tumours in non-smokers. They concluded that:

“*p53* mutations in lung cancer from smokers carry highly significant fingerprints of exposure to tobacco smoke components, in particular BaP (Benzo-[a]-Pyrene). These fingerprints are not found in nonsmokers”.⁶

From the evidence we have seen, it appears that the tobacco companies’ own research anticipated and sought to challenge Hernandez-Boussard and Hainaut’s work. For example, PM secured an unpublished copy of the submitted abstract from their paper by May 8, 1998, prior to its publication that July.³⁸ Following the paper’s publication, Lorillard, another tobacco company based in the USA, funded studies to challenge Hernandez-Boussard and Hainaut’s findings. A 1999 Lorillard list of “potential areas for consideration” for new scientific projects includes “IARC *p53* database analysis” and comparisons of the “smoker lung tumor *p53* mutation profile” with the mutation profile associated with in-vitro B[a]P exposure.³⁹ In 1999, two Lorillard scientists, Robert Leverette and Robert Lake, submitted an abstract to the 2000 meeting of the American Association for Cancer Research arguing against the conclusions of Hernandez-Boussard and Hainaut. Through an analysis of published *p53* mutation sequences in human lung tumours, Leverette and Lake found a “nonrandom pattern of mutations”. They concluded that this pattern was likely caused by “inherent organ/cell type factors rather than specific exposures”.⁴⁰ The abstract was not accepted for publication at the meeting.⁴¹

Another study was carried out by Thilo Paschke, an employee of the Verband der Cigarettenindustrie (VdC), the German association of cigarette manufacturers, from at least June 1999.^{42,43} The VdC includes German companies as well as PM, BAT, RJR, Lorillard.⁴⁴ A June 13, 2000 e-mail from Paschke to Chris Coggins, Lorillard Senior Vice President of Research and Development, reports:

“I published my analysis of the [IARC *p53*] database at a German conference on environmental mutagenesis . . . and submitted it to a journal on mutagenesis. I’ll send you a preprint of the paper, if the referees accept it for publication”.⁴³

Paschke’s paper was published in the November, 2000, issue of *Mutagenesis*. Analysing changes in the classification of smokers and non-smokers made in revisions of the IARC database released after Hernandez-Boussard and Hainaut’s paper, Paschke argues against an increased rate of G to T transversions or increased frequency of mutations in *p53* codons 157, 248, and 273 in smoker versus nonsmoker lung tumours. He argued that confounders “such as histological tumor type and gender, age, and ethnic origin” may have influenced Hernandez-Boussard and Hainaut’s conclusions.⁴⁵

Paschke’s employment by the VdC is not acknowledged in his publication. He is listed as an

employee of the Analytisch-Biologisches Forschungslabor. The association of this laboratory with the German tobacco industry as the research arm of the VdC is known, but not specified in the article.⁴⁵ The journal did not, however, require either of these associations to be disclosed.

On Jan 12, 2001, Pierre Hainaut, with Magali Olivier of IARC, and Gerd P Pfeifer of the Beckman Research Institute in Duarte, CA, submitted a response to *Mutagenesis*.⁴⁶ They noted that Paschke used the IARC p53 database in a manner against the published recommendations for its use and concluded that: "since we do not know which references have been used by Paschke, indiscriminate inclusion of mutations in his dataset may partially explain what he sees as 'discrepancies'".⁴⁷

In addition to addressing these technical issues, Hainaut and colleagues noted Paschke's ties to the tobacco industry. Their response, as initially submitted to the journal stated that

"... the paper by Paschke comes from a private institute of the German Association of Cigarette Manufacturers which has a long and proven history of participating in campaigns by the tobacco industry to subvert the normal scientific process of the evaluation of effects of tobacco smoke."⁴⁶

James M Parry, editor of *Mutagenesis*, responded to Hainaut and colleagues:

"I am not willing to approve the publication of your... point about the scientific integrity of Dr. Paschke. I am not willing to allow the pages of *Mutagenesis* to be used for non-scientific purposes... I now intend to forward your reply to Dr. Paschke together with a copy of this letter and indicate that he may provide a response to your comments. However, in any response from Dr. Paschke I will request that he provides an acknowledgement to any financial support to his work."⁴⁸

Hainaut and colleague's response and Paschke's reply were both published in the November 2001 *Mutagenesis*.^{47,49} Paschke's reply again argues against a statistically significant difference between smoker and non-smoker p53 mutations, and cites a confounding effect of "systematic changes in smoking status data of identical entries" listed in serial versions of the IARC p53 database. Paschke included the following acknowledgement:

"My study on the IARC p53 database was funded by the Forschungsgesellschaft Rauchen und Gesundheit. The Forschungsgesellschaft gets its financial funds [sic] from the Association of the German Cigarette industry."⁴⁹

The tobacco industry's relationship with the editor of *Mutagenesis*

The editor of *Mutagenesis*, James Parry, himself had undisclosed ties to the tobacco industry during the time when Cooper and Krawczak's³⁷ and Paschke's⁴⁵ papers

were published in the journal. Parry, founding editor and executive editor of *Mutagenesis* from 1983 to 2002, has held research and consultancy contracts with PM and BAT.^{50,51} In 1986, he approached the Tobacco Advisory Council, a British consortium of tobacco companies, for funding of research on the in-vitro genotoxicity effects of cigarette tar.⁵² A 1993 memo from Richard Thornton, BAT Smoking Issues Manager, to Barry Bramley, then BAT Chairman, lists Parry as a consultant to BAT at a rate of £500 per day.⁵¹ In 1993, he received £6000 as a consultant to BAT's SRG.¹⁷ His connections to the industry appear to have continued at least until 2001, when he was budgeted by PM to have received the final portion of a three-year grant worth £46 150 for a project studying genotoxicity in carcinogenesis.⁵³

BAT sought to use its connection to Parry to its advantage in dealing with committees regulating tobacco in the UK. In June, 1988, Parry was scheduled to present his findings on the mutagenicity of tobacco smoke in relation to tobacco product variables, such as tobacco blend, to the UK Independent Scientific Committee on Smoking and Health (ISCSH).⁵⁴ The ISCSH provided research funding for Parry through the Tobacco Products Research Trust.⁵⁴ Reporting on a 1988 visit to Parry's research group, Eian Massey, group manager in biology at BAT, expressed concern that Parry's presentation would be viewed by the ISCSH in "too simplistic a way" and that, in turn, "the ISCSH may choose to emphasize product developments" based on these results.⁵⁴ In May, 1988, Richard Binns wrote a memo to other scientific advisers at BAT regarding Parry's upcoming presentation:

"If some guidance can be achieved by giving Parry some of your results then you should do so. Ask him to ensure that the results would be presented with his own, without specific reference to BAT."⁵⁵

Eian Massey subsequently wrote to Parry in a letter dated June 3, 1988:

"please find enclosed the chromosome aberration and Ames data on the comparison of smoke condensates... In presenting these along with your data to the ISCSH, we would be grateful if you would not make any specific reference to BAT."⁵⁶

The documents do not indicate whether Parry took the requested actions.

The documents we have seen show that Parry also took the initiative in proposing projects to tobacco companies. In a memo to INBIFO scientist Wolf Reininghaus on Dec 19, 1996, Ruth Dempsey, PM Worldwide Scientific Affairs, reported:

"I would like to pass on a suggestion from Jim Parry regarding research into p53 and response to the Dennisenko paper on BPDE. Jim suggested that it might be worthwhile [for someone] with the requisite knowledge, to access the Hollstein [IARC] p53 database and perform a full analysis of the information which

was so fleetingly referred to in the “Science” article . . . Would there be anyone at INBIFO who would be interested in doing this?”⁵⁷

In April, 2001, Parry’s undisclosed relationship with the tobacco industry was brought to the attention of Oxford University Press (OUP) by Curt Harris, editor of the OUP journal *Carcinogenesis* and co-founder of the IARC *p53* database.^{58,59} In April 4, 2001, Janet Boullin, Journals Editorial Director of Oxford University press, responded that:

“OUP is treating the problem of undisclosed conflict of interest in *Mutagenesis* seriously and a letter went to Professor Parry yesterday . . . the letter asks that all future items sent to us for publication in *Mutagenesis* should be accompanied by a conflict of interest statement from the authors. I have also asked that the editors themselves each complete a form and return them to me.”⁵⁹

In March 2003, Boullin stated:

“The conflict of interest statement was first introduced to the journal at the beginning of April 2001. All the editors at that time were asked to sign but not all did so.

JM Parry stepped down officially as Editor at the end of 2001.

All the current editors have signed the conflict of interest statement and we posted a statement to this effect on the *Mutagenesis* Web site in the second week of March 2002.”⁶⁰

The conflict of interest statement described above states only that the three current “Executive Editors declare that they have no involvements that might raise the question of bias in their roles as Editors of *Mutagenesis*”.⁶¹ Parry did not sign the statement in April 2001. According to the *Mutagenesis* website as of January, 2005, Parry remained on the editorial board of *Mutagenesis*.⁶¹ Members of the editorial board have never been required to sign the conflicts of interest statement.⁶² Parry’s financial ties to major tobacco companies had not been publicly acknowledged by *Mutagenesis* or its publisher, Oxford University Press.

Discussion

Tobacco industry strategies to respond to *p53* research involved multiple levels of action. From 1986 forward, tobacco companies such as BAT and PM, viewing *p53* research as a potential area of future regulatory or litigation concern, monitored and funded *p53* research both internally and at external institutions. Through its SRG, BAT funded *p53*-related research at the Marie Curie Institute. This research programme was carried out by prominent cancer scientists who were at the time co-editors of the journal *Oncogene*. Further, SRG practices did not require disclosure of funding by grant recipients in publications. Following the 1996 publication of Denissenko and colleagues’ report in the journal *Science*, tobacco companies planned and carried

Panel 2: From International Committee of Medical Journal Editors: uniform requirements for manuscripts submitted to biomedical journals (1997)⁶³

“Conflict of interest for a given manuscript exists when a participant in the peer review and publication process—author, reviewer, and editor—has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected. Financial relationships with industry (for example, through employment, consultancies, stock ownership, honoraria, expert testimony) either directly or through immediate family, are usually considered to be the most important conflicts of interest. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making . . . Participants in peer review and publication should disclose their conflicting interests, and the information should be made available so that others can judge their effects for themselves”

out research programmes that contradicted laboratory and epidemiological findings linking tobacco smoke to lung cancer through specific mutations in *p53*. We have identified two instances where research arguing against the connection between tobacco smoke and patterned *p53* mutations was undertaken and published by individuals with links to tobacco companies.^{37,45} Both papers were published in *Mutagenesis*, whose editor-in-chief, James M Parry, has an extensive, undisclosed history of working as a tobacco industry researcher and consultant. Lastly, according to company documents, in 1996, Parry suggested to PM that analysis of the *p53* database be used as a response to the findings of Denissenko and colleagues.

In the 1997 revision of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, the International Committee of Medical Journal Editors (ICMJE), an international advisory board, defines conflict of interest as appears in panel 2.

The Uniform Requirements are guidelines issued by the ICMJE, and journals are not obligated to comply with them. However, the ICMJE document goes on to specify that authors of all submitted manuscripts “are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work”. Concerning editors, the ICMJE states: “editors who make final decisions about manuscripts should have no personal financial involvement in any of the issues they might judge”. The ICMJE criteria were revised in 2001, and are nearly identical to the 1997 criteria.⁶³ While widely accepted, the ICMJE criteria are viewed by some

as a “narrowly defined” criterion for conflict of interest, which could also be more broadly extended to include grant funding.⁶⁴

During the period we examined, the practice of requiring authors to disclose potential conflicts of interest was not widespread in many basic science journals. In 1997, only 16% of 1396 “highly ranked” scientific and biomedical journals had conflict of interest policies for authors in effect.⁶⁵ Further, less than 1% of the articles published during that year in journals that had conflict of interest policies in place contained any disclosures of potential conflicts, suggesting either low rates of author financial interest in the subjects that were being published, or a lack of adherence to journal conflict of interest policies.⁶⁵

Nonetheless, our research demonstrates multiple examples of potential conflicts of interest on the part of journal authors and editors between 1998 and 2001 concerning research on tobacco effects on the *p53* tumour suppressor gene. The most important of these existed for James M Parry, then Executive Editor of *Mutagenesis*. Parry’s employment as a researcher and consultant for PM and BAT gave him a direct personal financial involvement in issues concerning tobacco genotoxicity. David N Cooper and Thilo Paschke, authors of submissions to *Mutagenesis* on tobacco effects on *p53*, did not disclose their involvement with the tobacco industry as sources of potential bias, presumably because the journal did not have in place a policy requiring them to do so. While the then-current ICMJE standards recommended full disclosure of such potential conflicts of interest, the absence of a formal disclosure policy at *Mutagenesis* allowed these potential conflicts to go unacknowledged.

Prior research has demonstrated that tobacco industry connections are a potential source of bias in tobacco-related biomedical and policy research. Barnes and Bero (1998) reported that review articles funded by the tobacco industry are 88 times more likely than non-industry studies to conclude that passive smoke is not hazardous to human health.⁶⁶ Scollo and colleagues (2003) examined all published studies on the economic effects of smoke-free policies on the hospitality industry and found similar results: 94% of the tobacco industry supported studies concluded a negative economic impact compared to none of the non-industry supported studies.⁶⁷ When Krawczak and Cooper³⁷ published their paper in 1998 and Paschke⁴⁵ published his paper in 2000, *Mutagenesis* did not have a conflict of interest or disclosure policy, despite publishing articles with important legal and regulatory implications.

Since 2001, *Mutagenesis* has begun a practice of publishing statements of conflict of interest from its authors and executive editors, but appears to have instituted no disclosure policy with regard to the editorial board. No acknowledgment has been made of

potential conflicts of interest on the part of James M Parry, who remained on the editorial board as of January, 2005.

The tobacco industry has an extensive history of working to find evidence to counter science linking smoking to adverse health events.⁴ Recent examples include efforts to challenge second-hand smoke (SHS) research conducted in the USA,⁶⁸ in Europe at the International Agency for Research on Cancer (IARC),⁶⁹ and in Japan by Takeshi Hirayama.^{70,71} In each case, the public stances of tobacco companies maintained controversy surrounding the negative health effects of smoking and SHS^{4,72} through a number of actions,⁷³ including funding scientists who wrote publications critical of scientific methodology linking SHS to disease,^{68,74} sponsorship of research which challenged the scientific evidence against SHS,⁷⁵ and creating an international scientific consultants programme to influence professional and public opinion on SHS.^{76–78}

Since the 1950s, tobacco industry funding of scientists, consultants, and editors often has occurred without acknowledgment of tobacco industry support,^{4,68,77,79} presumably because in many cases journals did not have a policy of requiring disclosure of such support. In the early 1990s, a number of tobacco companies paid as much as \$156 000 to 13 scientists to write letters to the editor disputing the link between smoking and disease in journals including *JAMA*, *The Lancet*, and the *Journal of the National Cancer Institute*.⁸⁰ Two tobacco industry consultants, John Todhunter and Gary Flamm, were paid \$25 000 for an article criticising the Environmental Protection Agency’s SHS regulatory review process in the *Journal of Regulatory Toxicology and Pharmacology (JRTP)*, where Flamm was a member of the editorial board.⁸⁰

Gio Gori, associate editor of *JRTP*, has been a paid consultant of the tobacco industry since 1980, and has testified on their behalf regarding smoking and health.⁴ He submitted invoices to tobacco industry lawyers for financial reimbursement for letters he wrote disputing the link between SHS and health outcomes in *JAMA*, *Science*, and the *Wall Street Journal*.^{81–83} Alvin R Feinstein of Yale University was the editor of the *Journal of Clinical Epidemiology* and wrote extensively on the inadequacy of statistical methods used to link SHS to deleterious health outcomes.⁸⁴ He also criticised the efforts to discredit the tobacco industry by public health advocates. He did not disclose that at the same time he was a tobacco industry consultant and the recipient of “special project” funding overseen by tobacco industry lawyers.⁸⁵

The direct aetiological link between tobacco-induced *p53* mutations and lung cancer is a potentially powerful tool that can connect a patient’s disease to its specific cause. Such a tool could be useful in litigation and regulation concerning tobacco use, as it provides genetic proof of the health effects of tobacco both for the

individual smoker and those exposed to second-hand smoke. This use of *p53* is demonstrated by a 1997 deposition of Philip T Cagle, a pathologist at the Baylor College of Medicine.⁸⁶ In his testimony for the trial of Dunn, et al versus RJR Nabisco, et al, Cagle describes molecular changes in a lung tumour taken from Mildred Wiley, a victim of lung cancer that plaintiffs argued was induced by SHS. Cagle cites Denissenko and colleagues as evidence that the G to T transversion in codon 157 of *p53* found in Wiley's tumour was related to tobacco smoke exposure.

The tobacco companies claim that they are now working with the public health community to "support a single, consistent public health message on the role played by cigarette smoking in the development of disease in smokers".⁸⁷ Their multifaceted response to *p53* research as recently as 2001, suggests that the industry has not changed its practices.

Further, our findings demonstrate a consequence of the lack of uniform adherence by journals to standards for disclosing and assessing conflicts of interest in biomedical research and publishing. While the ICMJE has outlined voluntary standards for conflict of interest disclosure,⁸⁸ at least one observer has noted that current editorial practices preclude a clear definition of when, as a result of competing interests, "the findings and interpretation of a particular study are rendered unsafe or, at the very least, too uncertain to be a substantive scientific contribution".⁸⁹ The extent of tobacco industry involvement in *p53* research and the potential conflicts of interest examined here provide an example of tobacco industry strategy to challenge the science linking smoking to adverse health effects. In our view, these activities challenge authors, editors, and users of scientific literature to be vigilant in demanding and maintaining rigorous standards for disclosing and evaluating potential conflicts of interest.

Contributors

All authors contributed to the formulation, drafting, and editing of this paper. A Bitton and M D Neuman located most of the tobacco industry documents.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

- Hahn WC, Weinberg RA. Rules for making human tumor cells. *N Engl J Med* 2002; **347**: 1593–603.
- Hollstein M, Sidransky D, Vogelstein B, Harris CC. *p53* mutations in human cancers. *Science* 1991; **253**: 49–53.
- Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. *Cancer Res* 1994; **54**: 5284–95.
- Glantz S, Slade J, Bero L, Hanauer P, Barnes DE. The cigarette papers. Berkeley: University of California Press, 1996.
- Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in *P53*. *Science* 1996; **274**: 430–32.
- Hernandez-Boussard TM, Hainaut P. A specific spectrum of *p53* mutations in lung cancer from smokers: review of mutations compiled in the IARC *p53* database. *Environ Health Perspect* 1998; **106**: 385–91.
- Hollstein M, Shomer B, Greenblatt M, et al. Somatic point mutations in the *p53* gene of human tumors and cell lines: updated compilation. *Nucleic Acids Res* 1996; **24**: 141–46.
- Anon. External Research Activities BAT CF. 1986. UCSF BATCo Document Library. Bates no 100993265/3268. <http://www.library.ucsf.edu/tobacco/batco/html/8100/8166/index.html> (accessed Oct 31, 2003).
- Thornton RE. Note for the Tobacco Strategy Group: Scientific Research Group (SRG). Dec 2, 1993. British American Tobacco. Bates no 201 773789/3793. <http://bat.library.ucsf.edu/tid/hvd40a99> (accessed Nov 18, 2004).
- Anon. Research & Development. List of smoking & Health Contracts. No year. British American Tobacco Company Guildford Depository. Bates No. 500874413/4415. <http://bat.library.ucsf.edu/tid/xa00a99> (accessed Nov 18, 2004).
- Thornton R. Smoke clue to cancer mutations in lung cells. Feb 1, 1993. British American Tobacco Guildford Depository. Bates no 500848379/8381. <http://bat.library.ucsf.edu/tid/eom00a99> (accessed Nov 18, 2004).
- Thornton R. Visit to Marie Curie Research Institute, Oxted. Oct 1, 1991. British American Tobacco Guildford Depository. Bates no 300535077/5078.
- Nature Publishing Group. Oncogene: editors. <http://www.nature.com/onc/editor.html> (accessed Jan 7, 2004).
- Jenkins JR, Rudge K, Currie GA. Cellular immortalization by a cDNA clone encoding the transformation-associated phosphoprotein *p53*. *Nature* 1984; **312**: 651–54.
- Jenkins JR, Rudge K, Chumakov P, Currie GA. The cellular oncogene *p53* can be activated by mutagenesis. *Nature* 1985; **317**: 816–18.
- Braithwaite AW, Sturzbecher HW, Addison C, Palmer C, Rudge K, Jenkins JR. Mouse *p53* inhibits SV40 origin-dependent DNA replication. *Nature* 1987; **329**: 458–60.
- Anon. Smoking and health and the regulatory environment. 1993. British American Tobacco Guildford Depository. Bates no 301152131/2137.
- Roe F. Future Directions for Health Research. Oct 14, 1993. British American Tobacco Guildford Depository. Bates no 500834002/4016. <http://bat.library.ucsf.edu/tid/fwi10a99> (accessed Nov 18, 2004).
- Tricker A. List of accountabilities for 1998. 1998. Philip Morris. Bates no 2060566276/6278. <http://legacy.library.ucsf.edu/tid/rld13e00> (accessed July 19, 2002).
- Tricker A. Trip report. Aug 31, 1998. Philip Morris. Bates no 2060570122/0142. <http://legacy.library.ucsf.edu/tid/zkb13e00> (accessed March 10, 2003).
- Cline M. [No title]. July 31, 1987. R J Reynolds. Bates no 506333805/3806. <http://legacy.library.ucsf.edu/tid/urn74d00> (accessed March 10, 2003).
- Anon. Notice of research grant. CTR Grant Number: 3676A. Development and characterization of tissue-specific *p53*-deficient mice. May 17, 1995. R J Reynolds Tobacco Company. Bates no 516887073. <http://legacy.library.ucsf.edu/tid/lnt82d00> (accessed Nov 18, 2004).
- Solana R. PM USA says new study merits careful review. Oct 18, 1996. Philip Morris. Bates no 2501708086. <http://legacy.library.ucsf.edu/tid/btq52d00> (accessed July 26, 2002).
- Broughton M. Press announcement. News from BAT Industries. Opening remarks to analysts, investors and journalists. Oct 30, 1993. Brown and Williamson. Bates no 536580403/0405. <http://legacy.library.ucsf.edu/tid/ojq71d00> (accessed Dec 15, 2002).
- R J Reynolds Tobacco Company. Comments on the Denissenko, et al, article in October 18 issue of Science. Oct 17, 1996. R. J. Reynolds. Bates no 522903922. <http://legacy.library.ucsf.edu/tid/oam70d00> (accessed Nov 10, 2003).
- Wakeham H. Acquisition of INBIFO. April 7, 1970. Philip Morris. Bates no 2023241498. <http://legacy.library.ucsf.edu/tid/dmy74e00> (accessed Nov 18, 2004).

- 27 Diethelm PA, Rielle J-C, McKee M. The whole truth and nothing but the truth? The research that Philip Morris did not want you to see. <http://image.thelancet.com/extras/03art7306web.pdf> (accessed Nov 19, 2004).
- 28 Mueller T. Technical review of the Science paper by Thomas Mueller. 1996. Philip Morris. Bates no 2060536361. <http://legacy.library.ucsf.edu/tid/lyj13e00> (accessed Nov 10, 2003).
- 29 Anon. Summary of Denisenko paper. Oct 18, 1996. Philip Morris. Bates no 2501708144. <http://legacy.library.ucsf.edu/tid/srq52d00> (accessed Nov 18, 2004).
- 30 Anon. Benzo (alpha) pyrene and p53 gene mutations. 1996. Philip Morris. Bates no 2060536353/6356. <http://legacy.library.ucsf.edu/tid/ojy13e00> (accessed July 26, 2002).
- 31 Anon. Review of 'Preferential formation of benzo(a)pyrene adducts at lung cancer mutational hotspots in p53'. Oct 18, 1996. Philip Morris. Bates no 2063645433/5494. <http://legacy.library.ucsf.edu/tid/jibu67e00> (accessed Nov 18, 2004).
- 32 INBIFO. P53 Adducts. 1997. Philip Morris. Bates no 2064275957/5973. <http://legacy.library.ucsf.edu/tid/ksd39c00> (accessed Nov 3, 2003).
- 33 Anon. Scientific Research Group Berlin. June 5 1991. UCSF BATCo Document Library. Bates no 400313781/3787. <http://bat.library.ucsf.edu/tid/enc00a99> (accessed Nov 18, 2004).
- 34 Thornton RE. Visit to USA and Canada—October/November 1991. Nov 25, 1991. British American Tobacco Guildford Depository. Bates no 400183616/3633.
- 35 Anon. Scientific Research Group. Oct 28, 1993. UCSF BATCo Guildford Depository. Bates no 400453510. <http://www.library.ucsf.edu/tobacco/batco/html/2000/2016/index.html> (accessed Oct 31, 2003).
- 36 Anon. Projected SRG Budget for 1993. 1993. Brown and Williamson. Bates no 510100034. <http://legacy.library.ucsf.edu/tid/okm93f00> (accessed July 26, 2002).
- 37 Krawczak M, Cooper DN. p53 mutations, benzo[a]pyrene and lung cancer. *Mutagenesis* 1998; **13**: 319–20.
- 38 Me R, Walk R. p53 Mutations in lung cancer abstract. 1998. Philip Morris. Bates no 2063644313/4317. <http://legacy.library.ucsf.edu/tid/koh67e00> (accessed July 26, 2002).
- 39 Anon. Potential areas for consideration. 1999. Lorillard. Bates no 83235092/5099. <http://legacy.library.ucsf.edu/tid/bqj62d00> (accessed Dec 15, 2002).
- 40 Lake R, Leverette R. [Abstract form] Analysis of missense point mutation patterns in TP53 of human lung tumors. Nov 1, 2000. Lorillard. Bates no 83355947. <http://legacy.library.ucsf.edu/tid/wbt62d00> (accessed Nov 10, 2003).
- 41 American Association for Cancer Research. 91st Annual Meeting. March, 2000. San Francisco, CA, USA.
- 42 Heller WD, Scherer G. Ad hoc-Arbeitsgruppe "Additive". June 1, 1999. Philip Morris. Bates no 2505448714. <http://legacy.library.ucsf.edu/tid/gtl05c00> (accessed Nov 18, 2004).
- 43 Coggins C, Paschke T. Verbandt paper/kein betreff. 2000. Lorillard. Bates no 98423092. <http://legacy.library.ucsf.edu/tid/imw64d00> (accessed Dec 15, 2002).
- 44 Hirschhorn N. Shameful science: four decades of the German tobacco industry's hidden research on smoking and health. *Tob Control* 2000; **9**: 242–48.
- 45 Paschke T. Analysis of different versions of the IARC p53 database with respect to G?T transversion mutation frequencies and mutation hotspots in lung cancer of smokers and non-smokers. *Mutagenesis* 2000; **15**: 457–58.
- 46 Hainaut P. [Letter to James M Parry]. Jan 12, 2001.
- 47 Hainaut P, Olivier M, Pfeifer GP. TP53 mutation spectrum in lung cancers and mutagenic signature of components of tobacco smoke: lessons from the IARC TP53 mutation database. *Mutagenesis* 2001; **16**: 551–53.
- 48 Parry JM. [Letter to P Hainaut] Mutagenesis-Discussion Forum. Swansea, UK; Feb 12, 2001.
- 49 Paschke T. Reply to the contribution of Hainaut, Olivier, and Pfeifer. *Mutagenesis* 2001; **16**: 555–56.
- 50 Anon. Scientific research review committee funding, 2000. Feb 28, 2000. Philip Morris. Bates no 2505592320/2321. <http://legacy.library.ucsf.edu/tid/wya19c00> (accessed March 9, 2003).
- 51 Thornton RE. SRG Consultants. May 17 1993. British American Tobacco Guildford Depository. Bates no 401015173/5174. <http://bat.library.ucsf.edu/tid/qhr61a99> (accessed Jan 7, 2005).
- 52 Nelmes A. Minutes of the informal TAC/ISC research liaison meeting on Monday 12 May 1986 at Rothmans International UK Limited, Aylesbury. June 2, 1986. Philip Morris. Bates no 2001209659/9663. <http://legacy.library.ucsf.edu/tid/vtt68e00> (accessed July 26, 2002).
- 53 Anon. Scientific Research Review Committee Funding. 1995. Philip Morris. Bates no 2505601172/1176. <http://legacy.library.ucsf.edu/tid/lhr25c00> (accessed Jan 7, 2005).
- 54 Massey ED. [Visit to Professor J M Parry, University of Swansea. April 27, 1998]. April 27, 1988. British American Tobacco Company Guildford Depository. Bates no 400461502/1504. <http://bat.library.ucsf.edu/tid/ckc30a99> (accessed Jan 7, 2005).
- 55 Binns R. [Memo Richard Binns to ED Massey regarding technical problems of in-vitro assays]. May 6, 1988. British American Tobacco Company Guildford Depository. Bates no 400461501. <http://bat.library.ucsf.edu/tid/bkc30a99> (accessed Nov 18, 2004).
- 56 Massey ED. [Letter from ED Massey to JM Parry regarding the chromosome aberration and Ames data on comparison of smoke condensates]. June 3, 1988. British American Tobacco Company Guildford Depository. Bates no 400461464. <http://bat.library.ucsf.edu/tid/wjc30a99> (accessed Nov 18, 2004).
- 57 Dempsey R. [E-mail to W Reininghaus] January Meeting. Dec 19, 1996. Philip Morris. Bates no 2505155752. <http://legacy.library.ucsf.edu/tid/ild56c00> (accessed Nov 11, 2003).
- 58 Hainaut P, Hernandez T, Robinson A, et al. IARC Database of p53 gene mutations in human tumors and cell lines: updated compilation, revised formats and new visualisation tools. *Nucleic Acids Res* 1997; **26**: 205–13.
- 59 Boullin JM. Mutagenesis [E-mail to P Hainaut]. Oxford, UK. April 4, 2001.
- 60 Boullin JM. Mutagenesis [Email to Mark Neuman]. Oxford, UK. 2003.
- 61 Mutagenesis. Editorial board. *Mutagenesis*. 2003. <http://www.oup.co.uk/jnls/list/mutage/edboards> (accessed Jan 7, 2005).
- 62 Boullin J. Mutagenesis [Email to Mark Neuman]. 2004.
- 63 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Ann Intern Med* 1997; **126**: 36–47.
- 64 Friedman LS, Richter ED. Relationship between conflicts of interest and research results. *J Gen Intern Med* 2004; **19**: 51–56.
- 65 Krinsky S, Rothenberg L. Conflict of interest policies in science and medical journal: editorial practices and author disclosures. *Science Eng Ethics* 2001; **7**: 205–18.
- 66 Barnes D, Bero L. Why review articles on the effects of passive smoking reach different conclusions. *JAMA* 1998; **279**: 1566–70.
- 67 Scollo M, Lal A, Hyland A, Glantz S. Review of the quality of studies on the economic effects of smoke-free policies on the hospitality industry. *Tob Control* 2003; **12**: 13–20.
- 68 Ong EK, Glantz SA. Constructing "sound science" and "good epidemiology": tobacco, lawyers, and public relations firms. *Am J Public Health* 2001; **91**: 1749–57.
- 69 Ong EK, Glantz SA. Tobacco industry efforts subverting International Agency for Research on Cancer's second-hand smoke study. *Lancet* 2000; **355**: 1253–59.
- 70 Hong MK, Bero LA. How the tobacco industry responded to an influential study of the health effects of secondhand smoke. *BMJ* 2002; **325**: 1413–16.
- 71 Ong E, Glantz SA. Hirayama's work has stood the test of time. *Bull World Health Organ* 2000; **78**: 938–39.
- 72 Francey N, Chapman S. "Operation Berkshire": the international tobacco companies' conspiracy. *BMJ* 2000; **321**: 371–74.
- 73 Samet JM, Burke TA. Turning science into junk: the tobacco industry and passive smoking. *Am J Public Health* 2001; **91**: 1742–44.
- 74 Muggli ME, Forster JL, Hurt RD, Repace JL. The smoke you don't see: uncovering tobacco industry scientific strategies aimed against environmental tobacco smoke policies. *Am J Public Health* 2001; **91**: 1419–23.

- 75 Drope J, Chapman S. Tobacco industry efforts at discrediting scientific knowledge of environmental tobacco smoke: a review of internal industry documents. *J Epidemiol Community Health* 2001; **55**: 588–94.
- 76 Muggli ME, Hurt RD, Blanke DD. Science for hire: a tobacco industry strategy to influence public opinion on secondhand smoke. *Nicotine Tobacco Res* 2003; **5**: 303–14.
- 77 Barnoya J, Glantz S. Tobacco industry success in preventing regulation of secondhand smoke in Latin America: the “Latin Project”. *Tob Control* 2002; **11**: 305–14.
- 78 Barnoya J, Glantz S. The tobacco industry’s worldwide ETS consultants project: European and Asian components. *Eur J Pub Health* (in press).
- 79 Rennie D. Smoke and letters. *JAMA* 1993; **270**: 1742–43.
- 80 Rampton S, Stauber J. Research funding, conflicts of interest, and the meta-methodology of public relations. *Public Health Rep* 2002; **117**: 331–39.
- 81 Gori G. Invoice for consultation services. March 14, 1992. Brown and Williamson. Bates no 568000027/0028. <http://legacy.library.ucsf.edu/tid/wvp33f00> (accessed Nov 10, 2003).
- 82 Gori G. Invoice for consulting services. July 2, 1993. Minnesota Tobacco Litigation. Bates no 2024329114/9115. <http://legacy.library.ucsf.edu/tid/oua35e00> (accessed Nov 18, 2004).
- 83 Borelli T. Wall Street Journal ETS Article. July 28, 1993. Philip Morris. Bates no 2046662947. <http://legacy.library.ucsf.edu/tid/gbd03e00> (accessed Nov 10, 2003).
- 84 Yach D, Bialous S. Junking science to promote tobacco. *Am J Public Health* 2001; **91**: 1745–48.
- 85 Gertenbach R. Special Project #135R1 & R2. May 5, 1988. Council for Tobacco Research. Bates no 025224. <http://legacy.library.ucsf.edu/tid/kv18aa00/> (accessed Nov 18, 2004).
- 86 Dunn, et al. vs RJR Nabisco, et al. Deposition of Philip T. Cagle M.D. 11/25/97. Transcribed by: O’Neal Probst Wells: Delaware County (Indiana) Superior Court: 18001-9305-CT-06, 1997: 1–182. <http://legacy.library.ucsf.edu/tid/uyd94c00> (accessed March 11, 2003).
- 87 Philip Morris USA. Health Issues. 2003. <http://www.philipmorrisusa.com/en/health-issues/addiction.asp> (accessed Jan 7, 2005)
- 88 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. 2001 <http://www.icmje.org> (accessed Jan 7, 2005).
- 89 Horton R. Passive smoking: agreeing the limits of conflict of interest. *BMJ* 2003; **327**: 503.