

## Scientific Integrity: implications of tobacco industry involvement in the conduct of research

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## The tobacco industry and the scientific community: internal documents

- tobacco industry has had long-standing relations with the scientific community
- release of internal memos in 1998
- Attorneys General of 46 states sign the master settlement agreement with the nation's seven major tobacco industry organizations
- Industry strategy to recruit scientists to promote a public relations agenda regarding health effects and secondhand smoke

## Scientific Integrity: Is Public Health Compromised by Tobacco Industry Affiliations?

- Failure to disclose the tobacco industry's role in research and inadequate disclosure of industry financial ties
- Two case studies
  - The "Japanese Spousal Study"
  - James Enstrom and the American Cancer Society's Cancer Prevention Study (CPS I)

## Methods

- Legacy Tobacco Documents Library, University of California, San Francisco. ([www.legacy.library.ucsf.edu](http://www.legacy.library.ucsf.edu))
- Documents provided by U.S. tobacco companies as required by the 1998 Master Settlement Agreement
  - 27+ million documents
- Search terms:
  - Hirayama Study
  - Japanese Spousal Study
  - ETS
  - Meta-analysis
  - Enstrom, Kabat, CIAR
  - CPS I, CPS II
  - Womble Carlyle
  - Shook, Hardy and Bacon

## The Hirayama Study

- 1981, Takeshi Hirayama publishes a cohort study examining the effect of passive smoking among non-smoking wives of smokers in Japan (BMJ)
- wives of heavy smokers had an up to 2-fold risk of developing lung cancer compared to wives of non-smokers
- Hirayama study: most frequently cited study in regulatory proceedings on the U.S EPA risk assessment of passive smoking
- The political influence of Hirayama's study motivates the industry to disprove Hirayama's conclusions

## The tobacco industry's response: the "Japanese Spousal Study"

- Japanese Principal Investigators: Honorary Principal Investigators
- Tobacco industry scientist Chris Proctor directs study but his contribution is never disclosed
- CIAR-Center for Indoor Air Research: Tobacco-sponsored research foundation funds project
- Ghost Authorship

8 DATE: 04/15/91 RPAGES: 05VPM9A  
 FROM: Bob Pages SPANISH: RUS0212A  
 TO: Steve Parrish  
 SUBJECT: Japan ETS Exposure Assessment Study

Dear Steve:

This may somewhat preempt a note that Tom Osdene will shortly be sending you, however, I want you to know what I think:

We recently received a copy of a research proposal from Chris Proctor of CIAR which was subsequently discussed at last week's CIAR Board meeting. It's for a study which is SIMILAR to the one Rupp is currently doing in Columbus, OH.

However, this one would be done in Japan. There are two Japanese listed as co-principal investigators. Chris Proctor would be a "behind-the-scenes" study director. The proposal is projected to cost \$250,000 and would be completed

recommended is that I help to fund this. It's exactly the type of study we need. It may be too late for EPA, etc., but it should still be done. I think there's a very good chance that it will generate data which shows that ETS exposure in nonsmoking Japanese women is not much different from that of European or US women -- contrary to what the apologists for Mirayama have been saying all these years.

there's a very good chance that it will generate data which shows that ETS exposure in nonsmoking Japanese women is not much different from that of European or US women -- contrary to what the apologists for Mirayama have been saying all these years.

It's -- it would be a mistake to go into on their nose (or without it, neither or not they want to help pay for it is essential.

I don't know whether or not, as yet, you've been "lobbied" about this by Rupp, et al. If not, you will be. If this can be done right, it's worth doing. Rupp is apparently going to try to go through their international folks to get their share of the money -- the folks in Winston don't have the \$ (so they say). Can Parrish get the \$ ??

I'll be happy to try and answer any questions you have after you've read the stuff from Osdene.

Best regards,  
 Bob

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have the duplicate analyzed in the United States. Also, I am of the opinion that Dr. Chris Proctor might supervise this work but his presence should be low key and not appear in any of the publications, particularly since this is a Japanese study. In addition, I believe that Japan Tobacco Inc. must be advised

Three concerns: 1) This is NOT a project that should be funded by CIAR, Project'). 2) Proctor (and his fee) may be necessary to help get this done -- at least he has "hands on" experience with a similar study done in the UK -- but this should be a Japanese study: Proctor should not be a coauthor on any publication that comes out of it. 3) We must have the tacit o.k. of JTI to do

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 Bob

## CIAR: Center for Indoor Air Research

- foundation funded by the tobacco industry to support studies related to indoor air research, created in 1988
- mission was to fund high-quality objective research related to indoor air; maintained that they were an independent organization
- CIAR operated as a cover organization to promote tobacco industry agendas for scientific inquiry

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exposure in nonsmoking Japanese women is not much different from that of European or US women -- contrary to what the apologists for Mirayama have been saying all these years.

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One may wish to use a CIAR cover for this project. I believe it is very important that this be done with all due haste and could be of some appreciable

I don't know whether or not, as yet, you've been "lobbied" about this by Rupp, et al. If not, you will be. If this can be done right, it's worth doing. Rupp is apparently going to try to go through their international folks to get their share of the money -- the folks in Winston don't have the \$ (so they say). Can Parrish get the \$ ??

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## Publishing the Japanese Spousal Study

- Two grant proposals
- Industry modifies the original proposal submitted by Japanese investigators
- Industry instates project management of the study to their lawyers, Covington and Burling

PROPOSAL FOR AN APPLIED RESEARCH STUDY TO INVESTIGATE EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE IN NON-SMOKING JAPANESE WOMEN.

Project management would be undertaken by Covington and Burling. This would ensure appropriate detailed study design and performance, and enable timely report development. The project managers would remain remote from any scientific publications. They also would provide status reports to the supporting companies every two months.

Two Japanese scientists will be the principal investigators. Professor Jun Kagawa is an epidemiologist, physician and respiratory specialist currently teaching medicine at the

Mr. Peter Lee also will be asked to assist in reviewing the study design and in interpreting the data. It is not anticipated, however, that Mr. Lee will serve as a co-author of any of the publications flowing from the study.

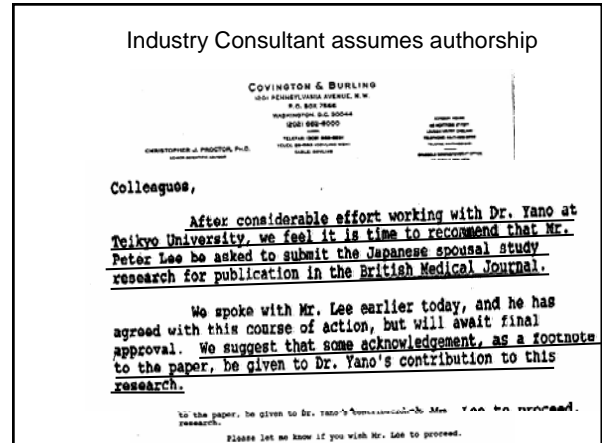
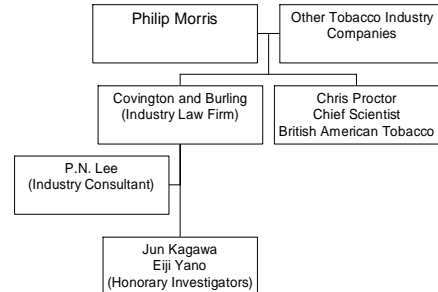
6. To compare exposure data and dietary information by living with a member and by rural, against urban habitation.

## Typical Research Protocol and Authorship

Principal Investigators  
Jun Kagawa  
Eiji Yano

Project  
Research Staff  
Assistants

## Tobacco Industry Authorship



Lee, P.N. "Marriage to a smoker" may not be a valid marker of exposure in studies relating environmental tobacco smoke to risk of lung cancer in Japanese non-smoking women. International Archives of Occupational and Environmental Health 1995, 67(5):287-94.

Acknowledgements I gratefully acknowledge financial support from several companies of the tobacco industry.  
I am extremely grateful to Dr. Eiji Yano of Teikyo University for assistance provided in Japan, and to Emu Efu Co. Ltd. for help in sample collection and analysis. I also thank Dr. John Fry for assistance in statistical analysis, Dr. Francis Roe for numerous helpful comments, and Mrs. Pauline Wassell and Mrs. Diane Morris for typing the various drafts.

## Contributor Criteria for Authorship: JAMA

- conception and design
- acquisition of data
- analysis and interpretation of data
- drafting of the manuscript
- critical revision of the manuscript for important intellectual content
- statistical expertise
- obtaining funding
- administrative, technical, or material support
- supervision

## Conclusion

- Tobacco industry goal: credible peer-reviewed publication
- Authorship standards disregarded in the process
- Calls into question the quality of the research

## James Enstrom and the American Cancer Society's Cancer Prevention Study (CPS I)

- Effectiveness of conflict of interest disclosure policies and a competing interests statement: a comparison using the industry documents
- Requirements for financial disclosure by the journal does not provide a full picture of tobacco industry involvement with study authors

## Introduction

- "Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960 – 1998." James Enstrom, Geoffry Kabat; May 2003, BMJ
- American Cancer Society cohort data circa 1959 (CPS-1 data set)
- Concluded secondhand smoke does **not** increase the risk of lung cancer or heart disease

## Thesis

- Enstrom and Kabat study sponsored in part by the tobacco industry's Center for Indoor Air Research (CIAR)
- Earlier studies show tobacco industry does not disclose their full involvement in industry funded research
- Internal memos document financial ties between the tobacco industry and authors of the study
- Enstrom and Kabat disclosure did not adequately describe the tobacco industry's role in their study

## American Cancer Society (ACS) and California Tobacco Related Disease Research Program (TRDRP)

- Disclosure acknowledged ACS developed the CPS-I dataset; but, head epidemiologist at ACS advised against the use of the CPS-I data set
- Study initially supported by TRDRP; funds terminated in 1994
- Disclosure suggests TRDRP's political climate was responsible for funding termination, and tobacco industry funds were accepted only **after** TRDRP resources became unavailable

## Enstrom: Early interactions with the tobacco industry

- 1975: first record of Enstrom approaching the tobacco industry for funding
- Enstrom requests the Council for Tobacco Research (CTR) to fund a study of cancer among Mormons living in the United States
- No record if proposal was ever funded

UNIVERSITY OF CALIFORNIA, LOS ANGELES

BERKELEY • BOSTON • BRIDGE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

ROBERT C. HOCKETT, Ph.D.  
 Research Director  
 The Council for Tobacco  
 Research--U.S.A., Inc.

SCHOOL OF PUBLIC HEALTH  
 LOS ANGELES, CALIFORNIA 90024  
 June 3, 1973

I am writing in response to your letter of May 20 in order to briefly describe my planned study of cancer among Mormons, in the hope that you can give me an appraisal of interest by the Council for Tobacco Research.

of these same groups and the general population. This should be helpful in assessing the possible role which other factors besides smoking play in the etiology of cancer. This work should suggest further retrospective or

In order to carry out this research, as outlined above, I would need about \$25,000 for each of two years. This would supplement the approximately

OF NOTE: Actual adherence to this life style varies greatly. Preliminary results indicate that...  
 background is needed, the results are summarized in the enclosed article and are soon to be published in detail in the journal CANCER.

## Enstrom: pro-tobacco or anti-tobacco?

- 1979: Enstrom publishes a review article that provokes criticism from the tobacco industry [Enstrom JE. Rising lung cancer mortality among nonsmokers. J Natl Cancer Inst 1979;62(4):755-60]
- Enstrom asserts "Environmental pollution including environmental tobacco smoke" may play a causal role in lung cancer risk

PHILIP MORRIS INCORPORATED  
 INTER-OFFICE CORRESPONDENCE  
 100 Park Avenue, New York, N.Y. 10017

To: Messrs. J. C. Bowling and A. Holtzman Date: June 1, 1979

From: J. E. Lincoln

Subject: Rising Lung Cancer Mortality Among Non-Smokers

The Enstrom article (copy attached) is of obvious interest. Its one negative feature seems to be the inclusion of environmental tobacco smoke as a possible cause of the increase in lung cancer among those who never smoked cigarettes. However, it seems to me the "passive smoking." If others here agree with my interpretation, we might consider challenging him on this point.

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cc: R. R. Millhiser

*copy to: M. Hill  
 I have advised Lincoln that this work is a waste of money & is giving us a view - JB*

## Developing a relationship with the tobacco industry

- 1990: Tobacco industry initiates contact with Enstrom to critique research on secondhand tobacco smoke
- Enstrom is asked by the industry to comment on work by Luis Varela, which concluded that secondhand smoke exposure was not associated with disease
- Enstrom declined to comment
- Enstrom uses Varela critique as an opportunity to request funding from Philip Morris to support his work

## Developing a relationship with the tobacco industry: CIAR

PHILIP MORRIS  
 INTER-OFFICE CORRESPONDENCE  
 100 Park Avenue, New York, N.Y. 10017

Regarding your inquiry about research funds, Philip Morris does not usually fund research projects. However, Philip Morris does support two independent research foundations: the Center of Tobacco Research and the Center of Indoor Air Research. If you like, I can provide you with the appropriate addresses so that you can apply to these organizations directly. If you have any further questions or if you would like to share your research ideas with me, please call.

in the workplace estimated up to the equivalent of 150 person years resulted in an odds ratio of 0.93 which, according to the authors, indicated "no evidence of an adverse effect of environmental tobacco smoke". Finally, the study also concluded that exposure in social settings resulted in a statistically significant inverse association between age and lung cancer.

The major difference between the Varela dissertation and the new study is the reported statistically significant association between exposure during childhood and development of lung cancer in adulthood. This was the only statistically significant result out of eleven sub-analyses conducted in this

## Industry Suspect

PHILIP MORRIS U.S.A.  
 INTER-OFFICE CORRESPONDENCE  
 Richmond, Virginia

To: Mr. Sam Nelson Date: November 26, 1990

From: Marvin Johnson

Smoking and Health: Have been asked by Bob PAGES to comment on some correspondence between Tom Borelli and James Enstrom of UCLA, who wrote a section of the 1983 Surgeon General's Report but now seems to have changed his mind on the smoking/mortality relationship. I say seems to have changed his mind because his writing is a little obtuse, and I'll have to read it again and do some calculations to know for sure. Found some additional information on the relationship

D. Product Line: With John Tardiff, wrote speech for Surgeon for November 9 outlining what we think would produce the greatest profit/consumption for PM. Looking at sources of potential smokers of the B&W Kings. (Johnson)

E. Product Line and Switching: Looking at smokers and switchers to and out of Winston, Marl, B&W and Virginia Slims. Prepared input/output charts. (Johnson)

F. Smoking and Health: Have been asked by Bob PAGES to comment on some correspondence between Tom Borelli and James Enstrom of UCLA, who wrote a section of the 1983 Surgeon General's Report but now seems to have changed his mind on the smoking/mortality relationship. I say seems to have changed his mind because his writing is a little obtuse, and I'll have to read it again and do some calculations to know for sure. Found some additional information on the relationship between smoking and lung cancer. (Johnson)

Enstrom's Dissertation which results in the same conclusion on the negative relationship. (Johnson)

CRB-07869

COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

**COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.**

TO: Scientific Advisory Board Executive Committee B.  
 Drs. Jakkil McAllister Pierce  
 Copies to Drs. Eisenberg, Ford, Hashim, Liantsi, Stone

2. ENCOURAGE formal application.

Attached are copies of key documents concerning this inquiry. Please indicate below your recommended action, and return ballot in the envelope provided.

*Is this manual? He's well educated, his proposal is somewhat interesting but - 25K is unrealistic to analyze even previous collected data. Maybe we better see it all. I'm worried about our supporting epidemiology of the tobacco problem. it can be done*

2 Oct 97  
 DATE

*[Signature]*  
 SIGNED

RIGHT!

COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

**COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.**

DATE: SEPTEMBER 13, 1997

TO: Scientific Advisory Board Executive Committee B.  
 Drs. Jakkil McAllister Pierce  
 Copies to Drs. Eisenberg, Ford, Hashim, Liantsi, Stone

1. DISCOURAGE formal application.

Attached are copies of key documents concerning this inquiry. Please indicate below your recommended action, and return ballot in the envelope provided.

1. DISCOURAGE formal application.  
 2. COMMENT on the proposal.

*The California tobacco control device group should fund this. It is not a study of tobacco but of effect of smoking cessation process*

10/4/97  
 DATE

*[Signature]*  
 SIGNED

### Strengthening the relationship with the tobacco industry

- 1997: Enstrom submits a proposal entitled "Relationship of low levels of active smoking to mortality" for funding to Phillip Morris Scientific Research Review Committee (SRR)
- Enstrom states "level of trust must be developed...commitment [needed] on your part to compete against the epidemiologic data and opinions that already exist regarding the health effects of ETS..." [2075873003]

### Minimizing University Oversight

Proposed Research on the  
 RELATIONSHIP OF LOW LEVELS OF ACTIVE SMOKING TO MORTALITY

submitted to  
 Philip Morris Research Center

Much of the methodology for the research done for this project can be used for the additional proposed research on passive smoking to be funded by the Center for Indoor Air Research.

The most appropriate means of funding needs to be determined, but an unrestricted gift to Dr. James E. Enstrom / UCLA with mutual understanding/trust would minimize University restrictions and eliminate overhead costs.

OVERALL OBJECTIVE  
 Obtain new results from four major epidemiologic cohorts on the relationship of mortality from lung cancer and other smoking-related causes to low levels of active smoking in order to assess the dose-response relationship.

SHORT COMMENTS to  
 Proposed Research on the  
 Relationship of Low Levels of Active Smoking to Mortality  
 submitted by J.E. Enstrom

Proposal

- The author asks for funding a follow-up of the U.S. veterans study. The aim is to establish a low dose response relationship for smoking and mortality.
- The existing data (name, sex, social security number, etc., and smoking status) will be provided to the applicant by NCI (Dr. A. Blair). Exact details of the data release have to be worked out.
- The applicant will obtain the cause of death (if not already available) by searches in national data bases.
- The rest of the research proposal deals with possible further research to be funded later.

Summarizing: The amount of money asked for seems rather high when considering the work proposed. The outcome, most probably, will not add much new scientific information. The applicant seems to have good connections/resources which might be useful in the future for other issues.

As the study relies on one questionnaire submitted 1957, it is probable that even more subjects have changed their smoking habits up to 1994. The inherent bias of the study is that misclassifications tend to drive the outcome in one direction: if a non-smoker is classified as occasional smoker, the RR will be stabilized at 1, but each heavy smoker classified as occasional smoker tends to increase the RR.

- Data already published give no clear dose-response relationship. It is highly unlikely that the follow-up will change the picture.
- As summary parameter the data already published (US-VI veterans) give a relative risk for lung cancer of 1.12 (95% CI: 0.89-1.42) for occasional smokers. If the additional subjects are numerically attributed with the same relative risks the new estimate would be 1.12 (0.82-1.36), i.e. the RR = 1 would be still included in the confidence interval.
- In order to get a relative risk higher than 1 with a confidence interval not including 1, i.e. being statistically significant, the new entrice (occasional smokers) must have an increase in lung tumor rate by a factor of 7.0 compared to those already evaluated.

PHILIP MORRIS INCORPORATED

480463  
 0000000480463  
 DATE 04/23/97

RICHMOND, VIRGINIA 23261  
 VOID AFTER 60 DAYS

PAY EXACTLY SEVENTY-FIVE THOUSAND 00/100\*\*\*\*\* DOLLARS CENTS

\*\*\*\*\*DOLLARS \*\*\*\*\*75,000/100\*\*\*\*\*

JAMES E ENSTROM/SCH OF PUBLIC HEALTH UNIV OF CA LOS ANGELES  
 10833 LE CONTE AVENUE  
 JAMES E ENSTROM/SCH OF PUBLIC HEALTH UNIV OF CA LOS ANGELES

THIS IS TOBACCO MONEY

480463 031100209 388 29156

## Research on Passive Smoking

- Enstrom submits pre-proposals to the tobacco industry's Center for Indoor Air Research (CIAR) to fund research related to secondhand smoke
- Proposes to analyze California CPS I cohort
- "Analysis will examine spousal smoking and death from lung cancer, coronary heart disease, and all causes"

## CIAR votes to fund CPS I analysis

- CIAR board discussions re: Enstrom and Kabat; "the possibility of their collaboration" **[May, 1997]**
- The CIAR board votes to fund passive smoking proposal **[November 1997]**
- The proposal for the CPS I analysis was funded for \$525,000 from June 1, 1998 through May 31, 2001 **[November 1997]**

## 'Flawed Science'—but good scientists

Comments on Proposal  
Environmental Tobacco Smoke and Mortality Among CPS I  
(J. E. Enstrom)

The proposal fails to distinguish between "ETS exposure" and "living with a spouse who smokes," makes light of the substantial loss-to-follow-up expected in this cohort, freely assumes adequate adjustment can be made for the non-representativeness of the initial cohort, underplays the impact of smoking cessation on the analyses, and is uncritical of positions established by the anti-smoking community.

The list of consulting authors (Heath, Kabat, Garfinkel) is impressive and should add credibility to interpretation of results.

- The proposal fails to clearly define the data upon which the planned analyses will be based. Apparently, some analyses will be based on the pre-existing follow-up data accumulated in 1960-72 from the "senior CPS I cohort" of married nonsmokers (approximately 90,000 male and 250,000 female subjects). Additional analyses will be based on this core data and on new follow-up data to be accumulated for 1973-99 on "recruited" CPS I subjects in the status of "never-smoking spouses, spouses of smokers, or non-smoking and non-spouse smokers."
- The list of consulting authors (Heath, Kabat, Garfinkel) is impressive and should add credibility to interpretation of results.
- Bottom line: The proposal is poorly written but addresses an important data resource that needs to be explored. It is concluded that this proposal be funded – but only after the proposal is rewritten to clarify the plan, population and hypotheses to be tested. A rewrite is essential to avoid wasting time and money on secondary issues, to avoid charges of "data dredging," and to force careful consideration of the issues that will confound or bias the results.

## Summary

- BMJ's policy: disclosure of relevant financial ties within the last 5 years
- Is Enstrom's disclosure accurate, given his long steady history of funding from the tobacco industry?
- Should journals stop publishing tobacco industry funded research?
- Enstrom study raises question of accepting tobacco industry money for academic research

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