

Tobacco Industry Efforts Undermining Evidence Linking Secondhand Smoke With Cardiovascular Disease

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Background—The scientific consensus that secondhand smoke (SHS) increases cardiovascular disease (CVD) risk by 30% is based on epidemiological and biological evidence. The tobacco industry has contested this evidence that SHS causes CVD, but how and why they have done it has not been described.

Methods and Results—About 50 million pages of tobacco industry documents were searched using general keywords and names of industry consultants and scientists. Tobacco industry–funded epidemiological analyses of large data sets were used to argue against an epidemiological association between SHS and CVD and smoke-free regulations, but these analyses all suffered from exposure misclassification problems that biased the results toward the null. More recent industry-funded publications report an increased risk of CVD associated with SHS but claim a low magnitude of risk. When early tobacco industry–funded work demonstrated that SHS increased atherosclerosis, the industry criticized the findings and withdrew funding. RJ Reynolds focused on attacking the biological plausibility of the association between SHS and CVD by conducting indirect platelet aggregation studies, exposure chamber experiments, and literature reviews. Although these studies also suffered from exposure misclassification problems, several produced results that were consistent with a direct effect of SHS on blood and vascular function. Instead, RJ Reynolds attributed these results to an unproven epinephrine-related stress response from odor or large smoke exposure, which supported their regulatory and “reduced-harm” product development efforts. Philip Morris’ recent “reduced-harm” efforts seem supportive of a similar corporate agenda.

Conclusions—The tobacco industry attempted to undermine the evidence that SHS causes CVD to fight smoke-free regulations while developing approaches to support new products that claim to reduce harm. The industry interest in preserving corporate viability has affected the design and interpretation of their cardiovascular studies, indicating the need for great caution in current debates about future tobacco industry regulation and development of reduced-harm tobacco products. (*Circulation*. 2007;116:1845-1854.)

Key Words: epidemiology ■ lipids ■ platelets ■ public policy ■ tobacco smoke pollution

The first epidemiological studies linking secondhand smoke (SHS) with heart disease were published in the mid-1980s,^{1,2} with reviews concluding that SHS caused cardiovascular disease (CVD) published in 1988³ and 1991.⁴ In 1992, the American Heart Association’s Council on Cardiopulmonary and Critical Care concluded that SHS was a “major preventable cause of cardiovascular disease and death.”⁵ With the accumulation of published literature, scientific and public health organizations have consistently concluded^{5–8} that SHS increases CVD risk by 30% and accounts for ≈46 000 nonsmoker deaths a year⁷; newer research strongly suggests a larger effect.⁹ Initially, many were concerned that the observed effect was too large, given the much lower dose of smoke a passive smoker receives than an active smoker. It is now clear that small exposures to tobacco smoke such as with SHS or smoking 1 or 2 cigarettes a day substantially affect heart disease risk because of the

nonlinear dose-response effects on platelet activation, endothelial dysfunction, and other factors.^{4,10–14}

The tobacco industry has contested the conclusion that SHS is dangerous because widespread acceptance of this fact builds support for smoking restrictions,^{15,16} which reduce cigarette consumption¹⁷ and thus industry profits. Beginning in 1988, the tobacco industry developed an “International ETS [environmental tobacco smoke, the industry’s name for SHS] Consultants Program” to “keep the controversy alive” on SHS by recruiting physicians and scientists to develop and promote viewpoints favorable to the industry.^{16,18} The industry’s now-disbanded Center for Indoor Air Research (CIAR) has been a mechanism for funding “special-reviewed” projects selected by lawyers and industry executives that support the industry position against smoking regulations.¹⁹ (CIAR has, however, been essentially reconstituted as the Philip Morris External Research Program.^{20,21}) The tobacco indus-

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try's efforts to subvert scientific conclusions on SHS have been previously described for lung cancer^{15,22–24} and sudden infant death syndrome.²⁵ The tobacco industry used similar strategies to undermine the evidence that SHS causes CVD to fight smoke-free regulations while later developing approaches to support new products that claim to “reduce harm.”

Methods

Between September 2005 and December 2006, we searched ≈50 million pages of previously secret internal tobacco industry letters, memos, and scientific reports made public as a result of litigation against the tobacco industry and available at <http://legacy.library.ucsf.edu>, <http://ltdlftd.library.ucsf.edu>, <http://bat.library.ucsf.edu>, and <http://tobaccodocuments.org>. Standard search methods began with general keywords “ETS and cardiovascular” and “ETS and heart” and the names of relevant industry consultants and executives (beginning with LeVois, Layard, Lee, Sanders, and Smith). Searches were narrowed using Boolean operators and snowball techniques for surrounding reference (Bates) numbers of related documents.²⁶ More than 5000 documents were reviewed, yielding 47 highly relevant documents. We also searched PubMed to verify whether tobacco industry consultants had published their work.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Use of Consultants to Criticize Conclusions That SHS Causes CVD

In September 1991, the Occupational Safety and Health Administration (OSHA) issued a “Request for Information” on regulating indoor air pollutants, including SHS.²⁷ The Tobacco Institute, the tobacco industry's now-disbanded lobbying arm, was concerned that OSHA “is unlikely to receive any information supportive of the industry's ETS position unless the industry provides it.”²⁸ The industry had already agreed on the position²⁹ that the epidemiological and biological evidence did not support the conclusion that SHS caused CVD. The Tobacco Institute funded several projects for “Addressing Epidemiologic Studies of ETS Health Effects,” including 2 by established industry consultants specifically designed to counter conclusions that SHS caused CVD. An analysis of the literature on ETS exposure and risk of lung cancer and CVD by Maurice LeVois was funded at \$10 000. Its objective was “to demonstrate that the ETS studies taken as a whole do not support the conclusion that ETS exposure in any setting is associated with increased risk of disease.”²⁸ The objective of the second, an analysis of the literature on ETS and CVD by Joseph Wu that was funded at \$20 000, was “specifically to refute the claim by Stanton Glantz and William Paimley [in their *Circulation* review⁴] that ETS is a cause of CVD in nonsmokers.”²⁸ Wu of New York University Medical College had helped organize the tobacco industry-funded McGill University symposium³⁰ in 1989 that concluded that the relationship between SHS and CVD was not worth studying. Maxwell Layard, another industry consultant, was later added to LeVois for literature analysis.³¹

Tobacco industry consultants continued to publish criticisms of the epidemiological literature on SHS and CVD. In 1992, industry consultant Nathan Mantel^{32,33} published a criticism of the 1991 Glantz and Parmley⁴ *Circulation* review

in the *Journal of Clinical Epidemiology*, whose editor was industry consultant Alvan Feinstein.³⁴ (Glantz and Parmley responded to Mantel's arguments in an adjoining article.³³) In 1995, another industry consultant, Gio Gori,³⁴ argued in *Regulatory Toxicology Pharmacology*³⁵ (whose editorial board included Gori starting in 1993³⁶) that SHS doses were too small to have a CVD effect and that confounders were not adequately controlled for in epidemiological studies.

Early Action Against Industry-Funded Work Showing SHS Accelerates Atherosclerosis

Animal experiments have contributed to the explanation that the unexpectedly large effect that SHS has on CVD is due to effects on platelet and arterial endothelium function,^{4,8,13} including those funded, but later criticized, by the tobacco industry. The tobacco industry's CIAR sought to study the effect of SHS on cardiovascular function³⁷ and contracted with Arthur Penn of New York University Medical Center for \$545 955 from 1990 to 1994 to study the question, “Does ETS Promote Arteriosclerosis or Act as a Co-Atherogen?”³⁸ Early progress reports³⁸ prepared by CIAR noted that Penn's studies did not demonstrate increased atherosclerosis in cockerels exposed to SHS. However, in September 1992, CIAR noted Penn found that plaque size significantly increased in cockerels exposed to sidestream smoke.³⁸ Penn published his results in *Circulation* in October 1993, stating that sidestream cigarette smoke inhalation from 5 cigarettes per day (total suspended particulate [TSP], 7.5 to 8.5 mg/m³) for 16 weeks accelerated the development of atherosclerosis.³⁹ Although the tobacco industry had funded and approved the protocol, the unfavorable results (from the industry's perspective) led Chris Coggins, an inhalational toxicologist at RJ Reynolds (RJR), to write a letter to *Circulation*,⁴⁰ criticizing the Penn study for using TSP levels that were 300 times higher than average measurements between smoking and nonsmoking homes (as measured by an industry consultant's⁴¹ study⁴²); Penn responded⁴³ that exposure levels were only 20 times higher than measurements in public places and only double if measuring carbon monoxide. The CIAR internal progress report expected Penn to perform his next study at a lower “relevant, typical ETS level found indoors (≈1 order of magnitude lower TSP than the original study)” and anticipated sidestream smoke exposures of 1200 and 600 μg/m³ TSP.³⁸ In March 1994, Penn presented results at a toxicology meeting reporting even SHS exposure from 1 cigarette per day (TSP, 2.5 mg/m³) for 16 weeks accelerated atherosclerosis.³⁸

In March 1994, a CIAR internal progress report noted these results and stated that CIAR would discontinue funding Penn since he performed the study at a higher TSP than contracted.^{38,44} Penn published his second article in *Circulation* in September 1994,⁴⁵ including a statement that carbon monoxide levels of the exposure chamber were at or below levels observed in 4 bars. (No Letters to the Editor were published.) Penn published a final experiment in *Circulation* in February 1996 demonstrating that 1,3-butadiene from SHS accelerated plaque development.⁴⁶ Coggins published another letter⁴⁷ criticizing the experiment for not using real-world values, and Penn responded⁴⁸ that the purpose of the experiment was to

determine whether this component of smoke even affected plaque development.

In a *Science* news interview⁴⁹ about Penn's findings, RJR's Coggins suggested the cockerels developed the plaques because of the stress of being in a smoky environment. Penn refuted this suggestion by saying the cockerels were docile in the cages like "pet rocks."⁴⁹ Possibly in response, Philip Morris' [PM] contract research laboratory in Germany INBIFO/CRC⁵⁰ considered comparing an isolated stressor, like a noise or restraint, to SHS in developing atherosclerosis,⁵¹ but we could not find any results from such a project. This alternative hypothesis that stress, not SHS, caused CVD changes would be expanded in other RJR experiments (described below in Attacking Biological Plausibility: RJR Experiments).

Funding Epidemiological Literature Concluding SHS Does Not Cause CVD

An April 26, 1994, meeting of the CIAR Board of Directors, which included Lorillard, RJR, PM, and the law firms Covington & Burling and Shook, Hardy, & Bacon, recognized the important policy impact of the evidence that SHS caused CVD but remained uncertain on how to proceed, particularly in areas relating to blood coagulation and platelet aggregation.⁵² CIAR considered research proposals from industry consultants on exposing humans to short- and long-term SHS and measuring cardiovascular function, including cardiac catheterization, exercise treadmill, platelet aggregation studies, heart rate variability, and metabolic studies,^{53,54} but this work does not appear to have been funded. Instead, as described below, CIAR focused on analyzing large epidemiological data sets.

The First Cancer Prevention and National Mortality Followback Survey Studies

Two months later, John Rupp, a lawyer from Covington & Burling who helped orchestrate the tobacco industry's worldwide response to the SHS issue,^{16,18} wrote⁵⁵ to the CIAR Executive Director and Board Chair about a \$50 000 proposal by consultants LeVois and Layard examining the association between spousal smoking and heart disease using the American Cancer Society's Cancer Prevention Studies (CPS-I and CPS-II) data sets. The work was submitted to OSHA and later to a scientific journal.⁵⁵ Layard⁵⁶ also proposed a separate study using the National Mortality Followback Survey (NMFS) to examine CVD deaths in passive smokers, noting in his proposal that preliminary analysis found no statistically significant results.

Both the LeVois and Layard⁵⁷ study of the American Cancer Society's CPS data sets and the Layard⁵⁸ analysis of the NMFS were published in the February 1995 issue of *Regulatory Toxicology and Pharmacology*, acknowledging PM⁵⁷ and CIAR⁵⁸ as funders. Both articles concluded that spousal smoking did not elevate the risk of heart disease in never smokers and that publication bias led to others' conclusions that SHS caused heart disease.

The 2 consultants' studies^{57,58} have been criticized^{7,59–62} for designs that bias results toward the null because of exposure misclassification. Both studies compared "never" exposed to spousal smoking with "any" exposure, which does not distinguish between current and former smokers. Because the cardiovascular risks of smoking decline rapidly with

smoking cessation,^{63,64} effects of past exposure would have substantially disappeared for spouses of former smokers. Furthermore, the CPS-I data set was built between 1959 and 1972, when SHS was so pervasive that even people married to never smokers were exposed to SHS (ie, many in the "control" group were actually exposed to SHS and misclassified as unexposed).^{60,61} The NMFS data set also had exposure misclassification and design problems: Information on smoking was obtained from next of kin by mail; the comparison group included only deceased persons; and a disproportionate number of ethnic minorities and young people had died.^{7,62}

The industry ignored these problems, instead concentrating on the fact that these studies were based on large data sets. When a 1995 review was published in the *Journal of the American Medical Association*¹⁰ updating the conclusion that SHS caused heart disease, the Tobacco Institute issued a statement criticizing the review by stating that "the two largest and most representative studies" did not support the review's conclusions and had been ignored by the authors.⁶⁵

These exposure misclassification biases were further demonstrated in a more careful analysis⁶⁰ in 1996 of the CPS-II data used by LeVois and Layard.⁵⁷ Steenland et al⁶⁰ excluded former smokers from the definition of spousal exposure to SHS and did not use the CPS-I data set because of the exposure misclassification problem. The resulting analysis revealed a 20% statistically significant increase in CVD risk associated with SHS. Despite the reanalysis by Steenland et al,⁶⁰ the UK Tobacco Manufacturers' Association, an industry trade group, continued to argue⁶⁶ that the 2 industry-funded studies^{57,58} should not have been excluded from a major review¹¹ and UK Scientific Committee on Tobacco or Health report⁶⁷ (analogous to a US Surgeon General report) that concluded that SHS caused CVD. In 1999, tobacco industry consultants Francis Roe and Peter Lee published "Environmental Tobacco Smoke Exposure and Heart Disease: A Critique of the Claims of Glantz and Parmley" in *Human and Ecological Risk Assessment*,⁶⁸ acknowledging an increase in CVD associated with spousal smoking but arguing that excluding the 2 industry-funded CPS⁵⁷ and NMFS⁵⁸ studies weakened the association. Using Lee's findings,⁶⁹ PM argued, as part of its successful opposition to the UK Health and Safety Commission's proposed workplace smoking regulations, that SHS did not increase CVD.⁷⁰

By 2000, PM's Worldwide Scientific Affairs Group Director Ted Sanders⁷¹ accepted that the Steenland et al⁶⁰ reanalysis, by excluding former smokers, had invalidated the 2 consultants' studies.^{57,58} However, Sanders' agenda on SHS and CVD was consistent with previous industry arguments, seeking to continue analyzing existing epidemiological data because "the quality of many of these studies is suspect," "reviews on this subject fail to evaluate this issue in an objective manner," and "the weaknesses of the epidemiological data" needed to be documented.⁷²

The Second Analysis of CPS-I

In 2003, Enstrom and Kabat⁷³ published in the *British Medical Journal* a second CIAR-funded analysis of CPS-I on SHS and tobacco-related mortality, examining never-smoking adults exposed to a smoking spouse, and concluded

that no statistically significant associations with mortality existed. The tobacco industry publicized the Enstrom and Kabat work around the world.⁷⁴ The study⁷³ was criticized for repeating the same exposure misclassification error as that by LeVois and Layard,⁵⁷ despite having been specifically warned by the American Cancer Society that it was inappropriate to use CPS-I for SHS studies.⁶¹ (An analysis of tobacco industry documents revealed that the *British Medical Journal* financial disclosure requirement was not adequate to give readers and reviewers an appreciation for the authors' long-standing relationships with the tobacco industry and the fact that the study was a "special project" funded by industry lawyers and executives outside the peer review process.²⁴) Both the California Environmental Protection Agency⁷ and the US Surgeon General⁸ subsequently discounted the Enstrom and Kabat study⁷³ in their evaluations of the health effects of SHS because of the problem in CPS-I with exposure misclassification.

In a 2006 PM-funded meta-analysis of SHS and cardiovascular mortality, Enstrom and Kabat⁷⁵ did conclude that SHS was associated with a statistically significant increase in cardiovascular mortality risk, albeit smaller than the consensus estimate (5%⁷⁵ versus 25% to 30%⁸), in *Inhalation Toxicology* (Its editorial board includes Lorillard and RJR representatives⁷⁶). This lower relative risk is due to the examination of only US cohort studies, including the 2 industry-funded CPS-I analyses^{57,73} despite the negative biases introduced by widespread exposure misclassification. (The CPS-I data set is large, so including these negative results will lower the pooled relative risk estimate.) The authors⁷⁵ acknowledged that the non-US studies tended to report higher risks but have 1 sentence stating that inclusion of the non-US studies did not "materially alter" the summary relative risks for the US results, even though their results differed from the risk estimates produced by non-tobacco-funded sources by a factor of 6.

Attacking Biological Plausibility: RJR Experiments

At the April 1994 meeting of the CIAR Board of Directors discussing next steps for the industry on SHS and CVD,⁵² RJR representatives advocated concentrating on biological plausibility issues.⁷⁷ RJR Research and Development initially planned to study SHS effects on atherosclerosis and cardiovascular function⁷⁸ but by 1992 (when Penn reported to CIAR that SHS increases atherosclerosis³⁸) focused on thrombogenesis⁷⁹ projects that suggest epistemological diversion to support their regulatory and product development efforts. Biomarker experiments using urinary thromboxane and prostacyclin as indirect measures of platelet aggregation were proposed for OSHA to calculate a permissible exposure limit for SHS and CVD.⁸⁰ (RJR qualified its proposal by stating that data on SHS did not demonstrate a health risk, but the assumption was necessary for developing regulation.⁸⁰) Atherothrombotic measurements (eg, lipids, platelets) would help inform RJR "reduced-harm" product development.^{81,82} Stress caused by SHS odor or irritation (which the industry was trying unsuccessfully to reduce in cigarettes⁸³) was presented as an alternative mechanism for the observed biological effects of SHS, an argument

suggested in 1994 by the Tobacco Institute⁸⁴ and expanded in subsequent RJR publications.⁸⁵⁻⁹¹

"Addressing Platelet Aggregation" With "Real World" SHS Exposures

RJR scientist Carr Smith led RJR's urinary thromboxane and prostacyclin studies in 1994, asking Gary Huber, a tobacco industry consultant⁹² and professor of medicine at University of Texas at Tyler, his opinion about these measurements as a reflection of platelet aggregation.⁹³ Smith reported to his Research and Development superiors that Huber and another colleague "believe that the variability of these measurements in smokers is fairly high, that it is unlikely that any release would occur even at the high dose, and even if a little release did occur the variability would mask the effect."⁹³ In previous industry-funded studies, urinary thromboxane and prostacyclin were measured in current smokers, which demonstrated high levels of variability.^{94,95} (Urinary thromboxane and prostacyclin are also only indirect measures of functional capacity of platelets, whereas aggregation is the gold standard because platelet behavior is observed directly.^{96,97} Urinary measurements of prostacyclin are complex because prostacyclin is produced in a variety of organs, including the kidney.⁹⁸ Because multiple mechanisms activate platelets,⁹⁷ even if 1 mechanism were disproved, it would not disprove the hypothesis that SHS enhances platelet aggregation.) Despite concerns of high variability, Smith reported in April 1994 to his Research and Development superiors that nonsmoker and smoker urine samples would arrive at RJR from the Verband, the German tobacco manufacturers' association,⁹⁹⁻¹⁰¹ to "address the allegation" that SHS exposure causes platelet aggregation¹⁰²; fewer urine samples were sent and used from the Verband original Munich study, but we found no reason why.

Smith et al⁸⁵ published a comparison of urinary thromboxane and prostacyclin in smokers, nonsmokers from nonsmoking homes, and nonsmokers from smoking homes in *Inhalation Toxicology* in 1998. (*Inhalation Toxicology*, with an editorial board⁷⁶ that includes coauthor David Doolittle, RJR Director of Biological Research, used RJR's Coggins to review the manuscript.¹⁰³ The same journal also published the 2006 PM-funded epidemiological meta-analysis of SHS and cardiovascular mortality.⁷⁵) Smith and colleagues⁸⁵ concluded that SHS exposure levels did not activate platelets in "typical home environments" because no difference in urinary thromboxane and prostacyclin was observed between nonsmokers from nonsmoking homes and nonsmokers from smoking homes. However, Smith's smoker "control group" did not demonstrate significantly elevated thromboxane relative to the 2 nonsmoker groups, which contradicted previous tobacco industry-funded literature^{94,95} demonstrating that active smoking was associated with thromboxane release. In the discussion, Smith and his coauthors acknowledged this inconsistency but argued that the active smokers in the study reacted differently because of large smoke exposures. The authors suggested that the large exposure would lead to an epinephrine release, causing platelets not to release thromboxane and resulting in a vessel wall reaction that released prostacyclin only.

Smith's study⁸⁵ misclassifies nonsmokers and misinterprets the results. The urinary cotinine levels of nonsmokers in nonsmoking households were 8.6 ± 10.8 (SD) ng/mL, indicating substantial SHS exposure, which is not surprising in Germany, which has no meaningful public smoking restrictions.¹⁰¹ (Serum cotinine is detectable at 0.05 ng/mL,¹⁰⁴ with urine levels ≈ 6 times higher than serum;¹⁰⁵ a serum cotinine level of 0.7 ng/mL indicates enough SHS exposure to have effects on CVD events.⁹) More important, Smith's interpretation that thromboxane release did not differ between active smokers and nonsmokers because of large smoke exposures may reflect the fact that the nonsmoker platelets were already sensitized to SHS because of high SHS exposure outside the home. The Smith study⁸⁵ did not reference a relevant study published 2 years earlier, a 1996 human exposure experiment¹⁰⁶ that demonstrated that repeated daily exposures to SHS over 1 week can elevate nonsmoker levels of serum thromboxane to be comparable to those of active smokers.

Chamber Experiment: Lipids, Inflammatory Markers, Lung Function, and Mutagenicity

Smith and another R&D colleague¹⁰⁷ conducted a \$203 500 environmental chamber study in 1995 and found that nonsmokers exposed to SHS had statistically significant changes in lipids, inflammatory markers, pulmonary function tests, and urinary mutagenicity.⁸⁶ The protocol exposed 20 healthy nonsmokers to filtered air over 5 days, except for day 3, which consisted of 7.33 hours of sidestream smoke (TSP, 179 $\mu\text{g}/\text{m}^3$).¹⁰⁸ After the exposure, low-density lipoprotein increased by 8% and total cholesterol increased by 2.6% in women; triglycerides increased by 15% and high-density lipoprotein (HDL) decreased by 5% in men; and the ratio of cholesterol to HDL for both sexes increased 3.2% and remained elevated for the next 2 days after exposure. Leukotriene B4 and prostaglandin E1 increased by 40%, and basophils decreased by 53%. Pulmonary function (forced vital capacity [FVC] and forced expiratory volume in 1 second [FEV₁]) declined and urinary mutagenicity (YG1024) increased. Rather than attributing the changes observed in this experiment to SHS, Smith⁸⁶ concluded that these changes were still "within clinically normal ranges" for lipid and pulmonary function measures and "within the range reported for minor changes in diet" for urinary mutagenicity.

Smith⁸⁶ argued that the triglyceride and HDL changes were "consistent with a 'stress' related epinephrine-induced mobilization of free fatty acids and a concomitant decrease in HDL," with the stress due to odor or high levels of smoke exposure, although no direct measurements of a stress response were included. Smith⁸⁷ also cited that stress caused the pulmonary function decline in his study, reporting his findings in response to a *Journal of the American Medical Association* study¹⁰⁹ on SHS exposure and pulmonary function. (The *Journal of the American Medical Association* authors¹¹⁰ replied that stress and increased catecholamines should instead have increased pulmonary function.) Smith⁸⁶ did not explain the leukotriene B4 and prostaglandin E1 changes in his study but considered them mediators of pulmonary inflammation in a subsequent research proposal.⁸² (Smith had not considered cardiovascular effects: Leukotri-

ene B4 is associated with vascular inflammation,¹¹¹ and prostaglandin E1 inhibits and deaggregates platelets.¹¹²) Although Smith and Sears⁸⁷ published their pulmonary and urinary mutagenicity findings¹¹³ in the open literature, we could not find publications of the lipids or inflammatory marker findings except in the conference proceedings⁸⁶ of the 1996 CORESTA (Cooperation Centre for Scientific Research Relative to Tobacco) Congress (a tobacco industry meeting).

Smith presented his findings at the 1996 CORESTA Congress as "one way of addressing the biological plausibility of the epidemiological association" of SHS and CVD.¹¹⁴ However, a RJR public relations official who attended the meeting reported to his superiors, "Neither Carr Smith nor Dave Doolittle received any questions after their presentations, from the stage, at breaks or at social events. It was almost as if the other companies were pretending the presentations had not taken place."¹¹⁵ RJR's results did not seem welcome by the other tobacco companies, with 1 representative suggesting that RJR must have needed lawyers to review the work.¹¹⁵ Smith and colleagues⁸² proposed follow-up human chamber exposure experiments to RJR's Human Research Review Committee for supporting RJR's OSHA permissible exposure limit proposal and "harm-reduced" product development, but we could not find any evidence of further work.

RJR Reviews Promoting Stress as an Alternative Mechanism

In a series of 3 reviews,^{88–90} Smith and colleagues promoted the hypothesis that epinephrine-related stress from odor or large smoke exposures, not the components of SHS, was the mechanism for platelet aggregation. Smith's first review, a 1998 meta-analysis of 56 platelet aggregation studies published in *Inhalation Toxicology*,⁸⁸ concluded that acute potentiation and chronic desensitization of platelets occur with smoking the first few cigarettes. Although the main platelet activation conclusions are consistent with other literature,⁶⁴ Smith hypothesized that the main mechanism resulted from a nicotine-induced release of epinephrine from the adrenals, as seen with physical stress. Smith's second review, entitled "Cardiovascular Effects of Odors" and published in *Toxicology Industrial Health*,⁸⁹ examined 15 studies (including 3 SHS exposure studies, 2 of which were Smith's earlier experiments^{85,86}) and concluded that adverse sensory reactions could lead to the release of catecholamines and stress hormones affecting physiological and biochemical measurements related to cardiovascular risk. Contrary to Smith's conclusions,⁸⁹ the third SHS exposure study¹¹⁶ did not demonstrate differences in plasma norepinephrine and epinephrine nor any physiological cardiovascular measurements except muscular sympathetic nerve activity.

In 2000, Smith's third review summarized his publications and arguments about stress in "ETS, Cardiovascular Disease and the Nonlinear Dose-Response Hypothesis"⁹⁰ in *Toxicological Sciences* and questioned previous^{6,67} conclusions that SHS caused CVD. Smith argued that lower smoke concentrations from SHS would activate platelets less than from active smoking because of a sigmoidal dose-response curve, and lower nicotine concentrations would not release epinephrine and sensitize platelets, Smith's main mechanism for

platelet aggregation.⁸⁸ A reviewer for the article questioned, "But what if ETS exposure is itself sufficient to place an individual up on the shoulder of the sigmoidal response curve?"¹¹⁷ This point, questioning Smith's entire argument, was not addressed when the manuscript was published.⁹⁰ Smith did make a new statement that the increases in leukotriene B4 and prostaglandin E1 in his chamber experiment⁸⁶ might reflect mast cells infiltrating plaque¹¹⁸ and affecting plaque stability, but he did not further discuss inflammation from SHS as a mechanism¹¹⁹ in CVD. (His original conference publication⁸⁶ did not discuss the findings.) The evidence supporting platelet aggregation as a mechanism of SHS causing CVD was not discussed, nor was the role^{12,64} of endothelial dysfunction and other factors.

Testing the Hormonal and Oxidative Stress Hypothesis With Real-World SHS Exposures

RJR initially planned in 1997 for a \$141 225 follow-up urinary thromboxane and prostacyclin study to include oxidative and hormonal stress measurements,¹²⁰ which would further support RJR's position that "exposure to the trace amount of ETS in 'real world' environments does not produce detectable biological effects in exposed nonsmokers," but discarded plans¹²¹ to work again with the German Verband.^{99–101} Terminating the collaboration may have been due to the US tobacco companies' litigation in which Verband documents became publicly available on the Internet.^{99,122} The Verband went on to compare levels of polycyclic aromatic hydrocarbons, which accelerates atherosclerosis in animals⁶⁴ and between smokers, nonsmokers from nonsmoking homes, and nonsmokers from smoking homes, and it published the study¹²³ in *Cancer Epidemiology, Biomarkers & Prevention*, concluding that diet and smoking, but not SHS, were major sources for polycyclic aromatic hydrocarbons. Similar to Smith's thromboxane and prostacyclin study,⁸⁵ which had used Verband samples,¹⁰² the serum cotinine levels of 0.71 ± 0.07 (SE) ng/mL in nonsmokers from nonsmoking households in the polycyclic aromatic hydrocarbons study¹²³ suggest widespread SHS exposure at levels high enough to affect CVD events.⁹

Instead of the Verband, RJR's Smith worked locally¹²⁴ with Thomas Fischer, a professor at the University of North Carolina at Chapel Hill who had done other work with Smith,^{85,88,90} to publish "Urinary Thromboxane, Prostacyclin, Cortisol, and 8-Hydroxy-2'-Deoxyguanosine [marker of oxidative DNA damage] in Nonsmokers Exposed and Not Exposed to Environmental Tobacco Smoke" in 2001 in *Toxicological Sciences*.⁹¹ The nonsmokers not exposed to SHS (self-reported as ≤ 15 min/d) demonstrated higher thromboxane levels than the nonsmokers exposed to SHS (self-reported as ≥ 5 h/d), but no other difference was observed for prostacyclin, 8-hydroxy-2'-deoxyguanosine, and cortisol. Smith concluded that platelet aggregation, as measured by thromboxane and prostacyclin, was not associated with SHS exposure.

Smith's study again misclassified nonsmokers and demonstrated inconsistent conclusions. The average serum cotinine for the nonsmokers not exposed to SHS was 0.2 ± 0.6 (SD) ng/mL,⁹¹ indicating substantial SHS exposure.¹⁰⁴ Review-

ers¹²⁵ of the manuscript for *Toxicological Sciences* questioned the variation in the thromboxane levels because the nonsmokers not exposed to SHS had a higher level of urinary thromboxane than the nonsmokers exposed to SHS. In the final published article,⁹¹ Smith acknowledged that these results were not consistent with previous literature^{94,95} suggesting that thromboxane was released with active smoking but suggested that the higher levels were due to an unknown stress (although Smith did not find that oxidative or hormonal stress was significantly associated). Reviewers¹²⁵ also noted a failure to comment on other relevant literature such as the 1996 human exposure experiment¹⁰⁶ that demonstrated that repeated daily exposures to SHS over 1 week elevated nonsmoker levels of serum thromboxane to those comparable to active smokers; this literature was not addressed in Smith's final publication.⁹¹

PM Interest in Biomarker Assays for "Reduced-Harm" Product Development

As debate over potential "reduced-harm" tobacco products developed among public health policymakers after 2000,^{126,127} PM planned with its Institute for Biological Research (INB-IFO) laboratory¹⁰⁰ to develop biomarker assays to evaluate new products.¹²⁸ Sanders planned to work with INBIFO¹²⁹ and a consultant¹³⁰ on SHS and CVD, hoping "to evaluate the evidence and suggest further studies to establish or eliminate the proposed mechanisms"¹³¹ under the auspices of PM's External Research Program rather than offer generalized critiques.¹³² In April 2002, the "Plausibility of the Association of ETS Exposure with CVD"¹³³ was a priority project for Sanders.

In August 2002, a PM scientist asked Sanders how SHS issues related to PM's "Harm Reduction Guidelines project" to evaluate future products.¹³⁴ Although Sanders still thought that the epidemiological evidence did not demonstrate an association with CVD or lung cancer, he privately acknowledged that SHS might have "real" CVD effects; he responded:

I am becoming more and more convinced that at least some of these effects are real. The purpose of this consultant's work is not to establish whether or not such effects are real, but to classify them in such a manner that we can focus on those that are likely to be the most important. Although it is quite possible, and even probably, that such effects have no long-term clinical significance, nevertheless, if they can be eliminated in a PREP [potentially reduced exposure product], that would be a positive development. . . Interestingly enough, it would appear, on the basis of very, very preliminary evidence at this point, that such effects, if they are indeed real, may be mediated by gas-phase components, particularly low-molecular-weight aldehydes.¹³⁵

Sanders' priority was not to establish "real" effects or "long-term clinical significance" but to demonstrate whether effects could be eliminated in a product. Sanders' comment about gas-phase components also has been suggested in other literature.⁶⁴

Discussion

This is the first article to describe how the tobacco industry initiated and funded scientific work to counter epidemiolog-

ical and biological conclusions that SHS causes CVD. The industry pursued this work initially to fight smoke-free regulations; later, the work also was done to promote allegedly “reduced-harm” products. Tobacco industry–funded epidemiological analyses^{57,58,73} of large data sets were used to argue against an epidemiological association between SHS and CVD, but these analyses all suffered from exposure misclassification problems that eventually even some in the tobacco industry⁷¹ recognized. More recent industry-funded publications^{68,75} report an increased risk of CVD associated with SHS but claim that the magnitude of the risk is far below the generally accepted 30% increase.^{7,8} When early tobacco industry–funded work demonstrated that SHS increased atherosclerosis,^{39,45,46} the industry criticized the findings for using smoke concentrations larger than that in the real world and withdrew funding. RJR focused on attacking the biological plausibility of the association between SHS and CVD by conducting indirect platelet aggregation studies, exposure chamber experiments, and literature reviews. Although many of the RJR studies also suffered from exposure misclassification problems, several^{85,86,91} produced results that were consistent with a direct effect of SHS on blood and vascular function. RJR, however, chose to interpret the cardiovascular effects associated with SHS as actually reflecting an unproven epinephrine-related stress response from odor or large smoke exposure (which the industry had tried unsuccessfully⁸³ to remove). RJR’s stress hypothesis supported their regulatory and “reduced-harm” product development efforts, and PM’s recent interest in these products seems similar in developing scientific work to support the viability of the industry rather than products with long-term clinical significance.

These industry efforts have not, however, prevented the scientific community from concluding that SHS causes CVD.^{7,8,67} It is now accepted that some of the key cardiovascular effects of SHS are nearly as large as those of smoking.^{12–14} However, the industry’s efforts to slow national regulation of SHS by OSHA—one of its original motivations for its efforts to challenge the conclusion that SHS caused CVD—were successful. Although OSHA conducted its own review and concluded that SHS increased the risk for lung cancer and CVD in 1994,²⁷ it withdrew its proposal for smoke-free workplaces in 2001 after the tobacco industry successfully delayed and weakened the proposal.¹³⁶ Because the OSHA proposal²⁷ addressed all indoor air pollution, not just SHS, the tobacco industry’s actions have repercussions on regulating other pollutants and environmental chemicals that have significance in the emergent field of environmental cardiology.¹³⁷

Simply eliminating SHS exposure through regulatory policies immediately reduces morbidity and mortality from CVD. Smoke-free workplaces reduce absolute smoking prevalence by 3.8% and reduce cigarette consumption among continuing smokers by ≈ 3 cigarettes a day.¹⁷ Implementation of smoke-free laws in public places and workplaces results in subsequent significant reductions in acute myocardial infarction hospitalizations^{138–141} by $\approx 27\%$.¹⁴² The California Tobacco Control program, which has a strong smoke-free component, significantly accelerated both the decline in cigarette consumption and cardiovascular mortality, with 59 000 fewer cardiovascular deaths estimated between 1989

and 1997.^{143,144} A model of the first-year benefits of making all unregulated workplaces smoke free in 1999, when $\approx 30\%$ workers were not covered by smoke-free policies,¹⁴⁵ estimated that such a policy would have prevented about 1500 myocardial infarctions and 350 strokes and resulted in nearly \$49 million in savings in direct medical costs.¹⁴⁶

The tobacco industry’s efforts to manipulate the scientific process, including the use of “special [scientific] projects” managed by lawyers, was a central element of the 2006 federal court ruling that the tobacco industry violated the Racketeer Influenced Corrupt Organizations Act (RICO) law to “defraud the public.”¹⁴⁷ The court did not, however, specifically address industry efforts to undermine the science on the CVD effects of SHS, perhaps because nothing had been published evaluating these efforts. As of 2007, PM and RJR still did not publicly acknowledge that their companies believe SHS causes disease. (These public positions contradict analyses of unpublished data from tobacco industry’s internal studies, which demonstrate that sidestream smoke from a burning cigarette [85% of SHS] is 4 times more toxic per 1 g TPM than mainstream smoke.¹⁴⁸ Their unpublished research also shows that as sidestream smoke ages, it becomes another 4 times more toxic than fresh smoke,¹⁴⁹ suggesting that aged sidestream smoke is an order of magnitude more toxic than fresh mainstream smoke.) For several years, PM has admitted that public health officials (but not PM itself) conclude SHS causes disease and that this concern is sufficient to warrant regulating smoking in public places¹⁵⁰; RJR’s Web site previously stated that although public health officials have reached this conclusion, the company believes SHS is unlikely to present any significant harm to otherwise healthy nonsmoking adults.¹⁵¹ After the federal RICO ruling,¹⁴⁷ RJR’s Web site was revised to state that adults should avoid exposing minors to SHS and that public policymakers should encourage the development of tobacco products that reduce harm or risk of serious disease.¹⁵² In addition, the court identified the Philip Morris External Research Program, which continues to fund cardiovascular research in universities, as an element of the continuing fraud. This fact has contributed to the decision by many universities to adopt policies to decline tobacco industry research funding.

Understanding the context in which the tobacco industry operates to preserve its corporate interests is important in evaluating the research funded by the tobacco industry on SHS, including that on CVD. The industry interest in preventing smoke-free regulations and supporting claims of “reduced-harm” products to preserve corporate viability has affected the design and interpretation of its scientific cardiovascular studies. The question of whether CVD effects, not just carcinogens, can be eliminated with the large number of chemicals in tobacco smoke must be on the forefront in the ongoing “reduced-harm” product debate,^{126,127} a debate that will intensify if the federal Food and Drug Association is granted authority to regulate tobacco products. The industry’s past and recent cardiovascular scientific activities indicate the need for great caution in current debates about future tobacco industry regulation and development of “reduced-harm” tobacco products.

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