

LETTER

Regarding “Phenylpropanolamine and Hemorrhagic Stroke in the Hemorrhagic Stroke Project”: Mercenary Epidemiology—Data Reanalysis and Reinterpretation for Sponsors With Financial Interest in the Outcome

Dear Editors:

Epidemiology shapes a sizable portion of American commerce. Drugs are licensed, chemicals are regulated, and industrial and automobile emissions are controlled by using results of the studies we perform. Epidemiologic studies also have a central role in determining whether polluters and manufacturers of dangerous products (or their insurance carriers) should be compelled to compensate people whose illnesses or injuries may have been caused by these products.

It is not surprising that companies threatened with increased financial burdens associated with regulatory compliance or civil liability hire scientists to challenge research findings that implicate their products. The result is a proliferation of reanalyses and reinterpretations of previously published studies, with the new work supported by parties displeased with the original results.

This describes a recent *Annals of Epidemiology* article by Stier and Hennekens (1) that questions the findings of the Hemorrhagic Stroke Project (HSP) that linked the over-the-counter drug phenylpropanolamine (PPA) with hemorrhagic stroke (2), published in the *New England Journal of Medicine* in 2000 (3). Stier is an attorney who represented the manufacturer of a PPA-containing product, and Hennekens was one of a group of consulting scientists hired by the manufacturers who provided some of the same concerns presented in the report to the US Food and Drug Administration (FDA) when the agency was deliberating whether to permit PPA to remain on the market.

Before it was withdrawn, PPA was used widely as a decongestant and appetite suppressant in many over-the-counter medications; six billion PPA doses were consumed annually (4). As early as the late 1970s, the FDA had received reports of hemorrhagic strokes in young women who had recently consumed PPA (5). PPA manufacturers commissioned the HSP after the FDA raised concerns about PPA-associated illness; the manufacturers selected the researchers (a team at Yale University) and approved the HSP research protocol.

In October 2000, the FDA's Nonprescription Drugs Advisory Committee held a public hearing in which the original study and consultants' critiques were presented and discussed; the Committee was virtually unanimous in its support of the proposition that there was an association between PPA use and hemorrhagic stroke (6). Shortly after this finding, the FDA asked the manufacturers to withdraw

the drug. The agency estimates that before it was withdrawn, PPA caused between 200 and 500 strokes per year among 18- to 49-year-old women (7).

The FDA is unlikely to ever permit the marketing of PPA because there is little evidence that its benefits outweigh its risks. Although PPA was used widely, its niche was immediately and successfully filled with other drugs that are inexpensive and apparently safer than PPA (8). The concerns raised by Stier and Hennekens (1) likely will never be confirmed or refuted by additional epidemiologic studies because an institutional review board would be reticent to approve new clinical trials for the drug given the apparent risk for hemorrhagic stroke and the existence of safe alternatives.

The debate over the link between PPA and stroke continues only in the legal arena: individuals claiming their illnesses are associated with their PPA consumption have sued PPA manufacturers. Although the Stier and Hennekens (1) critique of the HSP ostensibly is a commentary on the FDA's decision, it seems more plausible that it will be used not in the regulatory arena, but rather in the defense of PPA manufacturers in civil litigation.

Commissioning epidemiologists to reanalyze or reinterpret unfavorable findings is not new. In 1985, R.J. Reynolds Tobacco Co. hired several epidemiologists to critique studies by the asbestos industry and invent ways to attribute a greater proportion of lung cancer to asbestos, radiation, or any factors other than tobacco (9, 10). Cigarette companies successfully forced Dr Irving Selikoff, the nation's leading researcher on asbestos, to provide raw data from his studies of asbestos-exposed worker cohorts (11).

Attempting to use the same strategy, the tobacco industry hired epidemiologists in the early 1990s to reanalyze the initial studies linking environmental tobacco smoke and lung cancer, although the cigarette producers were stymied by lack of access to the raw data (12). Recent research using previously confidential tobacco industry documents, made public as a result of the extensive tobacco-related litigation, documents how the Philip Morris Co., a leading cigarette manufacturer, launched a legislative initiative to ensure its access to data from studies used in regulatory proceedings (13). One of the outcomes of this effort, which Philip Morris called its “sound science project,” was the “Shelby Amendment,” a one-sentence provision in a 4000 page appropriations bill that required investigators to provide raw data from federally

supported studies in response to Freedom of Information Act requests (14).

It was widely reported at the time that Senator Richard Shelby, for whom the legislation is named, introduced the provision because epidemiologists at Harvard University and the American Cancer Society refused to provide the electrical power industry with raw data from two large epidemiologic studies that reported increased risk for mortality associated with ambient particulate exposure (15, 16). The tobacco industry had recognized that their likelihood of success would be greater if they remained in the background and let other business groups push for the legislation (13).

For the most part, only government and government-funded studies are reanalyzed. Whereas corporate researchers have access to government-supported studies, there is no similar public access to privately funded science (17). (The PPA study is unusual in that manufacturers paid for both the original study and the critique.) In addition, reanalyses are expensive and only worthwhile to parties who face sizable financial risk if the findings of the original studies remain unchallenged. The overall impact of these factors is the disproportionate presence in the epidemiologic literature of reanalyses of government-supported studies with positive findings.

The occupational health literature is filled with reanalyses conducted with the intention of influencing government policy. Statistically significant elevated cancer mortality risks reported in the original research have disappeared in the recent reanalyses of studies of the mortality experience of workers exposed to beryllium (18) and chromium (19), two chemicals that currently are the subject of government rule making.

Federal support for occupational and environmental epidemiology is limited; it is rare for public resources to be devoted to conducting new studies that might help evaluate the validity of the criticisms raised in reanalyses. An important exception is benzene, a chemical that is both so toxic and so common in the environment that it continues to be an important subject of research. Although benzene exposure has been known for many decades to increase leukemia risk, it was a 1976 National Institute for Occupational Safety and Health (NIOSH) study (20) that served as the core of the risk assessment used in the current Occupational Safety and Health Administration occupational exposure limit of 1 ppm (21). The American Petroleum Institute sponsored two separate reanalyses of the exposure data in an NIOSH study. Both reanalyses disputed the NIOSH findings, concluding that elevated leukemia risk was associated only with far greater exposure levels (22, 23). However, newer findings from a joint US-China study of Chinese benzene-exposed workers reported elevated risk for leukemia, as well as for other blood disorders, at exposure levels less than those associated with leukemia in the original NIOSH study (24, 25).

For reanalyses and reinterpretations to be seen as valid and objective, the sponsors and investigators must afford honest and deliberate consideration of the complex issues involved (26). In response to the Harvard and American Cancer Society epidemiologists' resistance to providing unfettered access to their raw data, the Health Effects Institute agreed to organize an independent reanalysis of the two air pollution studies. The Health Effects Institute developed procedures specifically designed to preserve objectivity and transparency. The resulting analysis supported the findings of the original studies (27).

Too often, data reanalyses and reinterpretations are attempts to "manufacture uncertainty," a strategy used by polluters and manufacturers of dangerous products to avoid or delay regulation and civil liability (28, 29). These post hoc reanalyses must be viewed with skepticism unless they are done under transparent procedures that ensure the independence and integrity of the effort.

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