CHAPTER 4

Manufactured Uncertainty

Contested Science and the Protection of the Public's Health and Environment

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SINCE 1986, every bottle of aspirin sold in the United States has included a label advising parents that aspirin consumption by children with viral illnesses greatly increases their risk of developing Reye's syndrome. Before that mandatory warning was required by the U.S. Food and Drug Administration (FDA), the toll from this disease, for which the cause is unknown, was substantial: 555 cases reported in one year, 1980, and with many others probably missed, because the syndrome is easily misdiagnosed. One in three diagnosed children died.[1]

Today, less than a handful of Reye's Syndrome cases are reported each year. While the disappearance of Reye's Syndrome is often considered a public health triumph, it is a bittersweet one, because an untold number of children were disabled or died while the aspirin manufacturers delayed the FDA's regulation by arguing that the four scientific studies establishing the aspirin link were incomplete, uncertain, unclear. The industry raised seventeen specific "flaws" in the four studies and insisted that more reliable ones were needed.[2] The medical community knew of the danger, thanks to an alert issued by the Centers for Disease Control (CDC), but parents were kept in the dark. Despite a federal advisory committee's concurrence with the CDC's conclusions about the link, the industry issued a public service announcement claiming, "We *do* know that *no* medication has been *proven* to cause Reyes" (emphasis in the original).[3]

The manufacturer's campaign and the dilatory procedures of the White House's Office of Management and Budget delayed a public education program for two years and mandatory labels for two more.[4] Only litiga-

tion by Public Citizen's Health Research Group forced the recalcitrant Reagan administration to act. Thousands of lives have been saved—after hundreds had been lost.

Absolute certainty in the realm of medicine and public health is rare. Our public health programs will not be effective if absolute proof is required before we act; the best available evidence must be sufficient. Yet we see a growing trend that demands proof over precaution in the realm of public health.[5]

Few scientific challenges are more complex than understanding the cause of disease in humans. Scientists cannot feed toxic chemicals to people to see what dose causes cancer. Instead, we must harness the "natural experiments" where exposures have already happened in the field. In the laboratory, we can use only animals. Both epidemiologic and laboratory studies therefore have many uncertainties, and scientists must extrapolate from study-specific evidence to make causal inferences and recommend protective measures. Absolute certainty is rarely an option. Our regulatory programs will not be effective if such proof is required before we act; the best available evidence must be sufficient.

THE TOBACCO ROAD

Years ago, a tobacco executive unwisely committed to paper the perfect slogan for his industry's disinformation campaign: "Doubt is our product."[6] With tobacco, doubt turned out to be less addictive for the public than the leaf itself, and the industry finally abandoned its strategy.

I call this strategy "manufacturing uncertainty,"[7] and no industry manufactured more uncertainty over a longer period than the tobacco companies. Following a strategic plan developed in the mid-1950s by the public relations firm Hill and Knowlton—a firm that manufactured uncertainty on behalf of various industries over several decades—Big Tobacco hired scientists to challenge the growing consensus linking cigarette smoking with lung cancer and other adverse health effects. This industry campaign had three basic messages: cause-and-effect relationships have not been established; statistical data do not provide the answers; and more research is needed. As recently as 1989, a spokesperson appearing on national television dismissed claims that tobacco smoking

causes disease, declaring that "the causative relationship has not yet been established."[8]

The industry even started its own "scientific" publication, *Tobacco and Health Research*, for which the main criterion for articles was straightforward: "The most important type of story is that which casts doubt on the cause and effect theory of disease and smoking." Editorial guidelines stated that headlines "should strongly call out the point—Controversy! Contradiction! Other Factors! Unknowns!"[9]

Learning from tobacco's success, other industries have discovered that debating the science is much easier and more effective than debating the policy. Witness the debate over global warming. Many studies link human activity, and especially burning of carbon fuels, with global warming.[10] Waiting for absolute certainty that the accumulation of greenhouse gases will result in dramatic changes in the climate seems far riskier, and potentially far more expensive to address, than acting now to control the causes of global warming. Opponents of preventive action, led by the fossil fuels industry, attempted to delay the inevitable policy debate by challenging the science instead with a classic uncertainty campaign. I need only cite a memo from the political consultant Frank Luntz, delivered to his clients in early 2003. In "Winning the Global Warming Debate," Luntz wrote:

> Voters believe that there is *no consensus* about global warming within the scientific community. Should the public come to believe that the scientific issues are settled, their views about global warming will change accordingly. Therefore, *you need to continue to make the lack of scientific certainty a primary issue in the debate. . . . The scientific debate is closing [against us] but not yet closed. There is still a window of opportunity to challenge the science* (emphasis in original).[11]

There has been substantial media coverage of the political machinations behind the global warming debate, and the behavior of the tobacco industry has been well documented.[12] Less well known are the campaigns mounted to question studies documenting the adverse health effects of exposure to beryllium, lead, mercury, vinyl chloride, chromium, benzene, benzidine, nickel, and a long list of other toxic chemicals and pharma-

ceuticals. In fact, it is unusual for the science behind any proposed public health or environmental regulation not to be challenged, no matter how powerful the evidence.

Manufacturing uncertainty on behalf of big business has become a big business in itself. "Product defense" firms have become experienced, adept, and successful consultants in epidemiology, biostatistics, and toxicology. The work of these product-defense firms bears the same relationship to science as the Arthur Andersen Company's work for Enron and Worldcom did to accounting—or did, before it went bankrupt following the Enron debacle.

BERYLLIUM: NATIONAL DEFENSE OR "PRODUCT DEFENSE"?

The metal beryllium is extremely useful—and almost unimaginably toxic. Breathing the tiniest amount of this lightweight metal can cause disease and death. As a neutron moderator that increases the yield of nuclear explosions, it is vital to the production of weapons systems, and throughout the Cold War, the U.S. nuclear weapons complex was the nation's largest consumer of the substance. As a result, however, hundreds of weapons workers have developed chronic beryllium disease (CBD)—and not just machinists who worked directly with the metal, but also others simply in the vicinity of the milling and grinding processes, and often for very short periods of time.

As Assistant Secretary of Energy for Environment, Safety and Health from 1998 to 2001, I was the chief safety officer for the nuclear weapons complex, responsible for protecting the health of workers, the communities, and the environment around the production and research facilities. In 1998, the Department of Energy's (DOE) exposure standard had remained unchanged for almost fifty years, and there were hundreds of cases of beryllium disease in the nuclear weapons complex and in factories that supplied beryllium products.

The history of this original DOE beryllium standard is legendary. It was developed in a 1948 discussion held in the backseat of a taxi by Merril Eisenbud, an Atomic Energy Commission (AEC) industrial hygienist, and Willard Machle, a physician who was a consultant to the firm building the

Brookhaven Laboratory on Long Island, New York. Eisenbud discusses this history in his autobiography, noting that they selected the exposure limit "in the absence of an epidemiological basis for establishing a standard."[13] The AEC "tentatively" adopted a standard of 2 $\mu g/m^3$ in 1949, and then reviewed it annually for seven years before permanently accepting it.

When first implemented, the 2 $\mu g/m^3$ standard resulted in a dramatic decrease in new beryllium disease cases. But by 1951, Eisenbud recognized that "the distribution of the chronic form of beryllium disease did not follow the usual exposure-response model seen for most toxic substances" and hypothesized an immunological susceptibility.[14] Eventually, cases of CBD appeared among workers hired after the 1949 standard went into effect, and whose exposure appeared to be below the 2 $\mu g/m^3$ standard.[15] Moreover, CBD had been diagnosed in persons with no workplace exposure to the metal, including individuals who simply laundered the clothes of workers, drove a milk delivery truck with a route near a beryllium plant, or tended cemetery graves near a beryllium factory.[16]

When the Occupational Safety and Health Administration (OSHA) was established in 1971 to protect the health of workers in the private sector, it simply adopted the taxicab standard. By the 1980s, however, it was clear that workers exposed to beryllium levels well below the standard were developing the disease. As both the DOE and OSHA began the time-consuming legal process of changing their standards, the beryllium industry objected. At one public meeting, the director of environmental health and safety of Brush Wellman, the leading U.S. producer of beryllium products, asserted (according to DOE's minutes of the meeting): "Brush Wellman is unaware of any scientific evidence that the standard is not protective. However, we do recognize that there have been sporadic reports of disease at less than 2 $\mu g/m^3$. Brush Wellman has studied each of these reports and found them to be scientifically unsound."[17]

In 1991, Brush managers were told that if they were "asked in some fashion whether or not the 2 $\mu g/m^3$ standard is still considered by the company to be reliable," they should answer, "In most cases involving our employees, we can point to circumstances of exposure (usually accidental), higher than the standard allows. In some cases, we have been unable (for lack of clear history) to identify such circumstances. However,

in these cases we also cannot say that there was *not* excessive exposure" (emphasis in original).[18]

This was the industry's primary argument, and it was based on a flawed logic. Practically speaking, it was not difficult to go back into the work history of anyone with CBD and estimate that at some point in time, the airborne beryllium level must have exceeded the standard. Brush did this, and then reasoned that the 2 $\mu g/m^3$ standard must be fully protective since most people who had CBD had at some point been exposed to a higher level.

Yet, the ever-increasing number of CBD cases identified at facilities across the nuclear weapons complex, as well as in the beryllium industry's own factories, rendered the claim that the old standard was safe less and less plausible. In September 1999, Brush Wellman sponsored a conference, in collaboration with the American Conference of Governmental Industrial Hygienists, to bring "leading scientists together to present and discuss the current information and new research on the hazards posed by beryllium."[19] The papers were subsequently published together in an industrial hygiene journal.[20] Clearly, one purpose of the conference was to influence government standard setting on beryllium; at the time of the conference, DOE was a few months away from issuing its final rule and OSHA had signaled its intention to revise its outdated standard.

Several papers were presented by scientists employed by Exponent, Inc., the beryllium industry's product defense consultant, including a paper entitled "Identifying an Appropriate Occupational Exposure Limit (OEL) for Beryllium: Data Gaps and Current Research Initiatives." This paper promoted the industry's new rationale for opposing a new, stronger beryllium standard: that more research is needed on the effects of particle size, of exposure to beryllium compounds, and of skin exposure to CBD risk. The paper concluded: "At this time, it is difficult to identify a single new TLV [threshold limit value] for all forms of beryllium that will protect nearly all workers. It is likely that within three to four years, a series of TLVs might need to be considered. . . . In short, the beryllium OEL could easily be among the most complex yet established."[21]

After reviewing the public comments and the literature on beryllium's health effects, the DOE health and safety office concluded that, while more

research is always desirable, we had more than enough information to warrant immediate implementation of a stronger beryllium disease prevention standard. Over the industry's objections, we issued a new rule, reducing the acceptable workplace exposure level by a factor of ten.

Simultaneously, OSHA also recognized the inadequacy of its own standard[22] and announced its commitment to issuing a stronger one.[23] However, when the George W. Bush administration took office in 2001, the commitment to strengthening its beryllium rule was dropped from the agency's formal regulatory agenda.

In November 2002, OSHA implicitly accepted the industry's approach by issuing a call for additional data on the relationship of beryllium disease to, among other things, particle size, particle surface area, particle number, and skin contact.[24] In the few years since DOE issued its standard, however, researchers have published several epidemiologic studies that demonstrate that the 2 $\mu g/m^3$ standard does not prevent the occurrence of CBD.[25]

In addition to CBD, the scientific community widely recognizes that beryllium also increases the risk of lung cancer; several studies conducted by epidemiologists at the CDC support this conclusion.[26] In 2002, however, scientists at a product defense firm published a ten-year-old reanalysis of one of the CDC studies.[27] By changing some parameters, the statistically significant elevation of lung cancer rates was no longer statistically significant. (Such alchemy is rather easily accomplished, of course, while the opposite—turning insignificance into significance—is extremely difficult.) Not coincidentally, this particular firm had done extensive work for the tobacco industry.[28] The new analysis was published in a peer-reviewed journal—not one with much experience in epidemiology, but peer-reviewed nevertheless, and the industry now touts its study as evidence that everyone else is wrong.

And so it goes today, in industry after industry, with study after study, year after year. Data is disputed, data has to be reanalyzed. Animal data is deemed not relevant, human data not representative, exposure data not reliable. More research is always needed. Uncertainty is manufactured. Its purpose is always the same: shielding corporate interests from the inconvenience and economic consequences of public health protections.

PPA: THE TRICKS OF THE TRADE

In order to attract new clients, some product defense firms even brag about their successes. Until I wrote about it in *Scientific American*,[29] the Weinberg Group (another firm that had worked extensively for the tobacco industry) advertised on its website its contribution to the effort to oppose the FDA's belated clampdown on phenylpropanolamine (PPA), the over-the-counter drug that was widely used as a decongestant and appetite suppressant until the FDA forced it off the market.

Here is a short version of the PPA saga. Reports of hemorrhagic strokes in young women who had taken a PPA-containing drug began circulating in the early 1970s. Twenty years later, when the FDA finally raised official questions about the safety of PPA, the manufacturers rejected them. Eventually, a compromise was reached. The drug manufacturers would select an investigator—they selected the Yale University School of Medicine—and fund an epidemiologic study whose design would be approved by the FDA. In October 1999, the manufacturers and the FDA learned that the study confirmed the causal relationship between PPA and hemorrhagic stroke.[30] The study was published the following year in the *New England Journal of Medicine*.[31]

When they were initially alerted to the study's findings, did the manufacturers immediately withdraw this drug, which by then had annual sales of more than $500 million, but was responsible, according to an FDA analysis, for between 200 and 500 strokes per year among 18- to 49-year-olds?[32] No. Instead, they turned to the Weinberg Group to attack the Yale study, focusing on "bias and areas of concern."[33] The manufacturers recognized that the FDA would eventually force the drug off the market, but they stalled for almost a year, enough time to reformulate their products. And when the FDA finally requested manufacturers to stop marketing PPA in November 2000, the industry was prepared to ship reformulated products immediately.[34]

Amazingly, the Weinberg group boasted about this work on their website:

> Adverse Event Linked to OTC Product
>
> A pharmaceutical company retained THE WEINBERG GROUP to audit the results of a FDA-requested, industry-sponsored case-control study that linked their

over-the-counter (OTC) product and several others with a serious, life-threatening adverse event. There was a substantial concern from the FDA based on reports of adverse events that use of these OTC products would present a public health problem. The study was commissioned to answer the question of risk with a controlled investigation. According to the study investigators, the results of the study showed a strong association between these products and a severe, life-threatening adverse event. Epidemiologists at THE WEINBERG GROUP led experts and consultants to some of the other affected OTC companies, in an effort that included a reanalysis of the raw data from the case-control study, and an assessment of the study's methodological flaws. The unique ability of the experts at THE WEINBERG GROUP to combine their expertise in epidemiology and biostatistics with strategic thinking enabled them to lead the pharmaceutical company's effort in their dispute with the FDA.[35]

THE FUNDING EFFECT

The biomedical literature extensively discusses the "funding effect," a term used to describe the close correlation between the results of a study desired by a study's funders and the reported results of that study.[36] Recent reviews in leading biomedical journals found that pharmaceutical industry sponsorship was strongly associated with pro-industry conclusions.[37]

As researchers have examined the workings of the funding effect, it has become clear this is not the result of poorly done studies conducted by researchers apparently aiming for a preordained conclusion (although examples of this are not rare). The quality of the studies paid for by pharmaceutical manufacturers is at least as good and often better than ones they didn't fund.[38] This is not surprising, since drug makers have plentiful financial resources and more extensive experience conducting clinical trials. However, the failure to identify methodologic flaws that might explain the funding effect puzzled journal editors, who generally have strong scientific backgrounds and who pride themselves on their ability to identify poor-quality research.

What then explains the funding effect? It appears that the pharmaceutical industry is devoting sizable resources to the conduct of studies whose

results will increase sales, but will not necessarily provide the information physicians need to select the best drug for their patients. This has been summarized most clearly by Dr. Richard Smith, who recently retired as editor of *British Medical Journal* (*BMJ*). Describing how it took him "almost a quarter of a century editing for the *BMJ* to wake up to what was happening," he wrote:

> Why are pharmaceutical companies getting the results they want? . . . The companies seem to get the results they want not by fiddling the results, which would be far too crude and possibly detectable by peer review, but rather by asking the "right" questions—and there are many ways to do this [see list below]. . . . There are many ways to hugely increase the chance of producing favourable results, and there are many hired guns who will think up new ways and stay one jump ahead of peer reviewers.[39]

Smith went on to provide a series of examples of methods used by pharmaceutical manufacturers to obtain the results they want from clinical trials (the following is a quote):

- Conduct a trial of your drug against a treatment known to be inferior.
- Trial your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple endpoints in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress—for example, reduction in relative rather than absolute risk.[40]

The funding effect has also been seen in studies that look at the toxic effects of chemical exposures. The disparity between the results of studies

examining the risk of lung cancer among beryllium-exposed workers discussed above is an example of the funding effect: three government-funded analyses find an elevated risk while the one industry-funded analysis (actually a reanalysis) does not.

An even more striking example in the toxicology literature is the debate over the effects of low-dose exposure to bisphenol A (BPA), an environmental estrogen used in the manufacture of polycarbonate plastic, a resin widely used in food cans and dental sealants. Exposure to BPA had been reported in some studies to alter endocrine function at very low doses. In response, the American Plastics Council hired the Harvard Center for Risk Analysis (HCRA) to conduct a weight-of-the-evidence review of the toxicology. The HCRA panel reviewed nineteen animal studies and reported that it found no consistent affirmative evidence of low-dose BPA effects.[41]

This conclusion was challenged by scientists who felt that the HCRA had chosen to examine only a minority of the 47 studies available at the time. These scientists reviewed the 115 studies that had been published through December 2004 and found results that differed markedly from the HCRA analysis.[42] As can be seen in Table 4.1, 90 percent (94 of 104) of the studies paid for with government funds reported an effect associated with BPA exposure; not a single one of the 11 corporate-funded studies found an effect.

TABLE 4.1 Biased outcome due to source of funding in low-dose, in vivo BPA research as of December 2004

	Number of studies and effect reported	
Source of funding	Harm	No harm
Government	94	10
Chemical corporations	0	11
Total	94	22

SOURCE: Adapted from F. S. Vom Saal and C. Hughes, "An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment," *Environmental Health Perspectives* 113 (2005): 926–933.

VIOXX: CONFLICTED SCIENCE AND ITS CONSEQUENCES

I am not presuming here that the scientists involved in manufacturing uncertainty knowingly promote deadly products. More likely, scientists, along with the corporate executives and attorneys who hire them, convince themselves that the products they are defending are safe, and that the evidence of harm is inaccurate, or misleading, or trivial.

This can be seen in the recent evidence on the cardiac effects of Vioxx (rofecoxib), Merck's blockbuster pain reliever that was taken off the market in November 2004, making headlines around the world. Even before the FDA approved Vioxx in May 1999, agency scientists reviewed data that suggested Vioxx could increase heart disease risk. Several independent scientists (that is, not on Merck's payroll) also raised red flags, but for the most part, the FDA ignored them. Then the results of a clinical trial appeared in early 2000, just a few months after the drug was put on the market, linking Vioxx with an increased risk of heart attack.

Merck had chosen naproxen (sold under the brand name Aleve) as the comparison treatment in the trial because aspirin, perhaps a more obvious choice, was known to lower cardiovascular disease risk, and the company didn't want its trial to find more heart attacks among the study participants who took Vioxx. But the results showed that participants who took Vioxx for more than eighteen months had five times the risk of heart attack as those taking naproxen.[43]

Merck's scientists faced a dilemma. They could interpret this finding to mean either that Vioxx increased heart attack risk by 400 percent or that naproxen was beneficial in reducing the risk of heart attack by 80 percent. When a double-blind trial using a placebo control found seven excess heart attacks per every thousand users per year, the correct interpretation was clear: Vioxx causes heart attacks. One FDA analysis estimates that Vioxx caused between 88,000 and 139,000 heart attacks—30 to 40 percent of which were fatal—in the five years the drug was on the market.[44]

Subsequent litigation has uncovered memos documenting that Merck executives were concerned about the increased risk of heart attacks

associated with Vioxx, but downplayed these concerns in their communications with physicians and resisted the FDA's efforts to add warnings to Vioxx's label.[45] It is hard to imagine that the drug maker's scientists were consciously promoting a product they knew would result in disease and death. At the same time, it is hard to imagine they honestly thought naproxen reduced the risk of heart attack by 80 percent. It is possible that their allegiances were so tightly linked with the products they'd worked on, as well as the financial health of their employers, that their judgment became fatally impaired.

A NEW REGULATORY PARADIGM

There are clear lessons from these repeated regulatory failures in recent years: a new regulatory paradigm is needed. Federal agencies must ensure that data and scientific analyses provided by manufacturers are independently verified. Opinions submitted to regulatory agencies by corporate scientists and, especially, the product defense industry must be taken as advocacy, primarily, not as science. Below are a few steps that begin to develop this new paradigm.

It has become apparent that some industry-supported research is never published because the sponsor didn't like the results. Following a series of alarming instances in which the sponsors of research used their financial control to the detriment of the public's health, a group of leading biomedical journals have established policies that make their published articles more transparent to commercial bias and that require authors to accept full control of and responsibility for their work.

These journals will now only publish studies done under contracts in which the investigators had the right to publish the findings without the consent or control of the sponsor. In a joint statement, the editors of the journals asserted that contractual arrangements allowing sponsor control of publication "erode the fabric of intellectual inquiry that has fostered so much high-quality clinical research."[46]

But the federal regulatory agencies that are charged with protecting our health and environment have no similar requirements. When studies are submitted to the EPA or OSHA, for example, the agencies do not have the authority to inquire who paid for the studies, and whether these

studies would have seen the light of day if the sponsor didn't approve the results. Federal agencies should adopt, at a minimum, requirements for "research integrity" comparable to those used by biomedical journals: parties that submit data from research they have sponsored must disclose whether the investigators had the right to publish their findings without the consent or influence of the sponsor.[47]

It is also important to recognize that the opinions of virtually any scientist can be clouded by conflict of interest, even if it isn't apparent to the scientist herself. Conflict of interest inevitably shapes judgment—and this must be factored into the consideration of the analyses and opinions of scientists in the employ of industry.

Public health is not well served by the unequal treatment of public and private science. While raw data from government-funded studies are generally available to private parties for inspection and reanalysis, enabling product defense experts to conduct post hoc analyses that challenge troubling findings, industry is under no obligation to release comparable raw data from their own studies. When private sponsors conduct research to influence public regulatory proceedings, these studies should be subject to the same access and reporting provisions as those applied to publicly funded science.[48]

Apologists for polluters and manufacturers of dangerous products commonly complain about government regulation, asserting that the agencies are not using "sound science." In fact, many of these manufacturers of uncertainty do not want "sound science"; they want something that sounds like science, but lets them do exactly what they want.

We all recognize that the scientific evidence is just one part of policy making. In shaping rules and programs to protect the public health and environment, decision makers also have to consider economic issues, moral values, and a host of other factors. In our current regulatory system, debate over science has become a substitute for debate over policy and the values on which policy should be based.

Opponents of regulation use the existence of uncertainty, no matter its magnitude or importance, as a tool to counter imposition of public health protections that may increase their financial burden. It is important that those charged with protecting the public's health recognize that the desire

for absolute scientific certainty is both counterproductive and futile. This recognition underlies the wise words of Sir Austin Bradford Hill delivered in an address to the Royal Society of Medicine in 1965:

All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8:30 next day.[49]

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