ARTICLE

Conflicts of Interest: Manipulating Public Health

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Abstract

Evaluating the potential health impacts of chemical, physical, and biological environmental factors represents a challenging task with profound medical, public health, and historical implications. The history of public health is replete with instances, ranging from tobacco to lead and asbestos, where the ability to obtain evidence on potential environmental hazards has been impaired and the publication of results delayed because of commercial interests. The burden of proof is heavy on those trying to change the status quo when that involves highly profitable industries. When evaluating potential hazards that are linked with industrial activities, it is often the case that only after proof of human or environmental harm becomes undeniable are steps finally taken to control or reduce future hazards. This approach has the net effect of delaying and postponing action, allowing dangerous practices to continue until health or environmental risks have become undebatable.

Key Words: *Public health; controversies; policies; tobacco.*

Public health research is tasked with the responsibility of figuring out how to predict harm in order to prevent damage from occurring. The predictive nature of the effort necessitates relying on simulations, models, and experimental findings to estimate risks so that hazards can be mitigated. As a matter of health policy, the burden of proof should rest on those who produce materials to demonstrate their safety at the outset, rather than resting on those who bear the health consequences of using such materials years later.

Identifying the nexus between exposures and disease remains a complex and confusing task.

Identifying the nexus between exposures and disease remains a complex and confusing task, especially because many chronic diseases have long latencies and vary with respect to host characteristics, including inter-individual variability, that affect the timing, nature, and magnitude of the eventual health consequences. For years, it was wrongly assumed that cancer-causing chemicals are able to lead to cancer only via direct genetic mutations. As a result of these assumptions, extensive efforts have focused exclusively on finding mutations in specific genes, an approach that is increasingly turning out to be flawed. Overall, recent analyses indicate that only 5–10% of all cancers are linked to inherited mutations; in the remaining 90–95%, such mutations were not described (Anand et al., 2008). Thus, most cases of cancer are thought to arise as a result of changes in gene expression that occur in the absence of mutations, and many of these are the result of environmental factors.

The ability of certain chemicals to cause cancer in the absence of mutations is best illustrated by nickel compounds, which do not appear to be mutagenic according to *in vitro* tests but are, nevertheless, carcinogens, as several epidemiological studies on animals and humans have shown (Doll, 1958; Ottolenghi et al., 1975; Kasprzak et al., 2003; Grimsrud & Peto, 2006). The higher prevalence of cancer of the nasal cavity of nickel workers was first reported by Bridge in 1933 (Bridge, 1933; Kasprzak et al., 2003). The ability of nickel compounds to cause heterochromatin formation and to epigenetically silence gene expression provides the mechanistic explanation for carcinogenesis, filling in a decades-long gap in understanding the molecular basis of diseases linked to exposure. This new understanding of epigenetic factors involved in the carcinogenesis of nickel salts illustrates that new mechanisms are constantly unveiled to explain long-known phenomena (Ellen et al., 2009).

Because harmful human health effects are often apparent long before the underlying mechanistic processes involved are understood, it is not uncommon for a long time to elapse until mechanisms are elucidated, if ever. In this respect, the example of thalidomide is illustrative. A therapeutic agent first synthesized in 1954, thalidomide was commercialized in 1957 and was subsequently used in >40 countries as a sedative and to treat morning sickness (Ito et al., 2011; Vianna et al., 2011; Lachmann, 2012). The first clinical case reports of congenital malformations caused by this compound were reported in 1961 and 1962 (McBride, 1961; Lenz, 1962). Understanding thalidomide teratogenicity has fascinated the community for almost half a century, but the first molecular target of its toxicity was discovered only in 2010 (Ito et al., 2010, 2011).

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Unfortunately, in recent years, as peer-reviewed articles have revealed adverse effects of commercial products, a classic and well-honed defensive public-relations strategy has evolved: the lack of known biological mechanisms that could account for any adverse effect is invoked as a way to reassure consumers that no harm could possibly occur. This flawed tactic, which has been successfully employed by several industries, does not serve public health well.

Smoking is, by now, well known for its complex adverse health effects. It will take many decades to unveil the mechanisms of action for at least a few compounds from the mixture of >4000 chemicals found in cigarette smoke (Richter et al., 2008). One of the earliest studies that linked smoking to cancer was published in 1939, and others followed in 1950 (Müller, 1939; Doll & Hill, 1950; Wynder & Graham, 1950). As early as 1928, a study underscored the high rate of smoking among lung cancer patients and raised the possibility that nonsmoking wives of smokers developed lung cancer by passively inhaling the smoke (Schönherr, 1928). Nevertheless, a 1984 memo by the well-funded Tobacco Institute mentioned the lack of known biological mechanisms with respect to the link to coronary heart disease (CHD) as grounds for undermining and challenging evidence that such an association was real. That memo noted that "Perhaps most important of all, no mechanism has been established to explain *how* tobacco smoke might cause CHD" (Legacy Tobacco Documents Library, 1984). As is well known by now, smoking is the strongest modifiable risk factor for CHD, which is a leading cause of death and the main cause of death by cardiovascular diseases worldwide (Lopez et al., 2006; Thom et al., 2006; Lluís-Ganella et al., 2009; Gaziano et al., 2010; Agüero et al., 2013). Using a similar strategy, companies that opposed the regulation of asbestos exposure noted that chrysotile asbestos cement does not pose any threat to human health, as there is "simply no mechanism whereby such damage could occur" (British Asbestos Newsletter, 2002–2003), a position that continues to be asserted by various pro-asbestos forces. Corporate funding of research in all these instances created a biased climate in which independent research was a scarcity (Davis, 2007).

When it comes to devising protective public health policies, demanding that mechanisms be proven before associations between a specific exposure and a given health outcome can be established constitutes an example of flawed reasoning, and places an often insurmountable burden on public health research. This is especially the case where some clinical or epidemiological evidence of human harm already exists.

At a time when public understanding of science is not high, it can be easy to mislead people about technical matters. Certain industries have historically invested considerable efforts in manufacturing doubt, magnifying uncertainties, undermining scientists who produce positive findings, and ensuring the widespread dissemination of information that confuses people. For example, a strategy used to deflect attention from lead paint toxicity was to blame children affected by lead poisoning who, it was argued, were "sub-normal to start with" (Rosner & Markowitz, 2007). Additionally, their parents and caregivers were also charged with providing insufficient supervision and inadequate parenting (Markowitz & Rosner, 2002; Bellinger & Bellinger, 2006; Rosner & Markowitz, 2007, 2008). At least 35 articles were published between 1904 and 1940 on lead paint poisoning in children, and ~4000 publications were reported to exist in 1939 on occupational lead poisoning (Rabin, 1989). Nevertheless, in 1979, when a landmark paper revealed that children with elevated dentin lead levels showed psychological and academic delay, several critical responses sent to the same medical journal questioned the methodology, stated that the "inference of causation […]seems unjustified by the data," and asked whether the possibility that distractible children could eat paint chips or other lead-containing materials is not "equally likely, or perhaps even more likely" (Kramer, 1979; Needleman et al., 1979).

"Doubt is our product" boasted a 1969 memo, at the time confidential, vividly depicting the tobacco industry's strategy of creating uncertainty and confusion about the adverse health effects of smoking (Legacy Tobacco Documents Library, 1969). Widely documented in the literature, the numerous strategies employed by the tobacco industry to use science as a form of public relations to undermine protective policies are part of an approach that we call *multi-layered deception*. These included casting doubt on studies showing that smoking is hazardous, funding research to counter and contradict those reports while concealing industry involvement through multiple mechanisms, deleting inconvenient research findings, influencing medical professionals, manipulating the hospitality industry to oppose and prevent smoke-free environments, and approaching funding agencies to curtail the funding of scientists who published inconvenient results (Dearlove et al., 2002; Hong & Bero, 2002; Neilsen & Glantz, 2004; Proctor, 2004; Bero, 2005; Bitton, 2005; Diethelm et al., 2005; Barnes et al., 2006; Landman & Glantz, 2009).

Another strategy to promote this dangerous product involved marketing cigarettes to teenagers as young as 14 years, recognizing that an earlier age of adoption resulted in a more powerful addiction (Josefson, 1998; Perry, 1999). "[…] if our Company is to survive and prosper, over the long term, we must get our share of the youth market" stated a 1973 cigarette company memo as part of a strategy to market new products targeted to younger segments of the population. In 1975, another document pointed out that "the brand must increase its share penetration among the 14–24 age group which have a new set of more liberal values and which represent tomorrow's cigarette business" (Legacy Tobacco Documents Library, 1973, 1975). Yet as far back as 1953, a tobacco industry chemist wrote, in a document summarizing 78 articles from the literature, that clinical studies "tend to confirm the relationship between heavy and prolonged tobacco smoking and incidence of cancer of the lung" (Legacy Tobacco Documents Library, 1953; Cummings et al., 2007). Nevertheless, a year later, an executive from the same company was quoted by the press saying that "there still isn't a single shred of substantial evidence to link cigarette smoking and lung cancer directly" (Minnesota Trial Court, 1998; Boyle et al., 2010).

An inter-office correspondence circulated in 1980, at a time when the harmful effects of smoking had already been known to tobacco officials for decades, again illustrates one of the many tactics intended to protect industry interests at the expense of human health: "We within the industry are ignorant of any relationship between smoking and disease" (Legacy Tobacco Documents Library, 1980). Finally, to exemplify the extent of the deceptive tactics employed by the tobacco industry, it suffices to compare the remarks made in 1963 by an industry executive, who noted that "nicotine is addictive…. We are, then, in the business of selling nicotine, an addictive drug," with the 1994 testimony that the CEO of the same company made before the U.S. Congress: "I do not believe that nicotine is addictive" (Legacy Tobacco Documents Library, 1963; Bero, 2005).

Smoking continues to be a major public health concern globally, in all segments of the population. Second-hand exposure places children and household members at risk of chronic bronchitis, heart disease, and lung cancer. Recent studies have confirmed that the damaging effects of smoking extend to nonsmokers in complex ways that have even more far-reaching implications than previously suspected. A newly emerging concept, "third-hand smoke," refers to a complex phenomenon in which tobacco-smoke contamination persists long after a cigarette is extinguished, due to toxins that are deposited in a layer on surfaces, such as the walls, carpets, or clothes, or remain in dust (Winickoff et al., 2009). These toxins may also interact with compounds from the environment, such as ozone or other oxidants, and form secondary pollutants (Matt et al., 2011a; Ferrante et al., 2013). Unlike second-hand smoke, which can be removed through ventilation, third-hand smoke persists on indoor surfaces (Ferrante et al., 2013). Another difference between the two is that while exposure to second-hand smoke occurs at high levels over short intervals, exposure to third-hand smoke occurs at low levels, but over long periods (Ferrante et al., 2013). Third-hand smoke pollutants were shown to persist for at least 2 months in the homes of smokers, even after they had moved out and the places were cleaned for nonsmokers to move in (Matt et al., 2011b). Also, the cars of smokers who smoked in their vehicles presented higher nicotine levels in the dust, on surfaces, and in the air than cars in which smoking was banned (Matt et al., 2008). Thus, indoor smoking can expose people to residues of toxins from tobacco smoke for a long time in the future.

Recent years have also marked important advances in understanding the molecular basis of the adverse effects that result from prenatal exposure to compounds from tobacco smoke. Nicotine was shown to cross the placenta and to accumulate in the fetus at concentrations >15% higher than the ones found in the mother (Lambers & Clark, 1996). Considering a recent study that showed a 12.8% overall prevalence of smoking during the last 3 months of pregnancy in the United States, prenatal exposure remains a significant public health problem (Centers for Disease Control and Prevention, 2012). Breton et al. (2009) reported that *in utero* exposure to maternal smoking is associated with gene-specific and global DNA methylation changes in children. In addition to decreased DNA methylation in a type of chromosomal repetitive elements, children of smokers presented increased methylation in several genes. Two genes that showed consistent changes are *AXL*, which encodes a protein involved in cell survival and relevant for cancer and the function of the immune system, and *PTPRO*, which encodes a protein involved in the development of the peripheral and central nervous system. A subsequent study reported that *AXL* hypermethylation in these children born to smoker mothers persists for years after their birth (Breton et al., 2011). In a genome-wide analysis of the placenta, Suter et al. (2011) revealed that smokers presented changes in the expression of 623 genes, opening intriguing questions about the long-term impact of prenatal exposure to smoke.

Adding to the evidence that links prenatal smoke exposure and the development of the nervous system, Toledo-Rodriguez et al. (2010) showed that exon 6 of brain-derived neurotrophic factor, a gene regulated by methylation and involved in brain development and function, showed higher DNA methylation in adolescents who were prenatally exposed to maternal cigarette smoking (Toledo-Rodriguez et al., 2010; Park & Poo, 2013). Finally, Maccani et al. (2010) revealed that the expression of several microRNAs that play critical roles in placental and fetal development changes in response to maternal smoking.

These recent discoveries on tobacco toxicity have come about, in part, because massive funds were made available after successful tobacco litigation efforts by state Attorneys General from 46 states and private litigators. These suits resulted in the 1998 Tobacco Master Settlement Agreement with Philip Morris Inc., R. J. Reynolds, Brown and Williamson, and Lorillard, the four largest U.S. tobacco companies. In exchange for exemption from personal liability claims on behalf of those who suffered damages from smoking, the settlement dissolved tobacco industry research groups, including the Tobacco Institute and the Center for Indoor Air Research, that had perpetuated disinformation by funding researchers around the world. This agreement provided for $206 billion for funding advertising campaigns to discourage smoking and to fund training and basic research on scientific questions.

Research on commercially profitable materials requires major funding and commitments. Therefore, it is absolutely crucial, particularly for exposures that are relevant in occupational and environmental contexts, to ensure independent funding. Only when that funding is secure can science be carried out without being subject to intense financial, political, and economic pressures. Had that been the case several decades ago, millions of lives would have been spared the damaging impacts of lead, asbestos, and tobacco. As we move into the 21st century, we need to establish safeguards that ensure the independence of funding and the training of scientists responsible for public health studies that aim to prevent, rather than confirm, harm.

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