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The Hazards of Genetically Engineered Foods

"Genetically Modified Foods: Breeding Uncertainty" (Schmidt 2005) overlooked many serious concerns about the environmental and health risks of this new technology. Potential problems from antibiotic-resistant genes used in gene-altered crops, risks from unintended effects of the genetic engineering process, the increases in pesticide use stemming from widespread planting of gene-spliced varieties—these and several other concerns were ignored or hardly mentioned in the lengthy article. Additional information on this topic is available from the Center for Food Safety (CFS 2000, 2004).

Instead, Schmidt's article states that "GM agriculture is here to stay" (Schmidt 2005) and gives readers the false impression that safety and regulatory issues have been adequately addressed by industry and government. Nothing could be further from the truth. For example, regarding the risk of allergies from gene-altered foods, Schmidt stated that biotech companies avoid allergy problems by avoiding genes from the most common allergens. However, in an editorial in the *New England Journal of Medicine,* Nestle (1996) pointed out that this approach leaves many uncertainties:

> Most biotechnology companies use microorganisms rather than food plants as gene donors, even though the allergenic potential of these newly introduced microbial proteins is uncertain, unpredictable, and untestable …. Because FDA requirements do not apply to foods that are rarely allergenic or to donor organisms of unknown allergenicity, the policy would appear to favor industry over consumer protection.

Schmidt (2005) went on to assert that after a 1993 study alerted them to the possibility of introducing allergens, biotech companies developed better screens and learned to abandon varieties that could not be deemed allergen-free. Far from abandoning a risky new variety 5 years after this study, industry marketed a new genetically engineered corn variety, despite warning signs that it might trigger allergies in people. Although it was registered only for nonfood uses, the altered corn, called StarLink, contaminated hundreds of food products sold in supermarkets nationwide and cost industry and farmers hundreds of millions of dollars to clean up. Aventis paid $110 million to compensate farmers for lost markets due to StarLink contamination, and analysts estimated that the company spent an additional $500 million to pay for losses to farmers, food processors, and grain handlers (Harl 2003; Jacobs 2003). Despite this and other troubling contamination episodes, such as those described by Gillis (2002), Nichols (2002), and Greenpeace (2005), the biotech industry continues to grow open fields of genetically engineered pharmaceutical crops (crops altered to produce experimental drugs or industrial proteins) that have never been assessed for their allergenic potential or other food safety issues.

Schmidt also ignored scientific concerns about the Food and Drug Administration's (FDA) approach to gene-altered foods. Millstone et al. (1999) criticized the idea of "substantial equivalence" that the FDA uses to evaluate genetically engineered foods, calling the concept "inherently anti-scientific because it was created to provide an excuse for not requiring biochemical and toxicological tests." In a letter published in *Nature Biotechnology*, Schenkelaars (2002) also derided the concept and noted that more appropriate testing methods would "systematically detect unintended changes in the composition of GM crops … as such changes may be of toxicological, immunological, or nutritional concern." A lawsuit the CFS brought against the FDA exposed documents from top level scientists throughout the agency, who warned that the FDA's equivalence-based policy was inadequate to protect against these kinds of unintended changes in gene-altered food (Alliance for Biointegrity 2004).

The purported benefits of gene-modified varieties should be examined against other agricultural approaches that have shown documented gains for food production and the environment. Schmidt (2005) cited a study of recent field trials of gene-altered rice in China that looked at a few dozen farms (Huang 2005). However, in one of the largest-ever studies of commercial rice growing, researchers found that thousands of Chinese farmers using agroecologic techniques saw yield increases of 89% while completely eliminating some of their most common pesticides (Zhu 2000). Other large-scale projects have shown that thousands of Chinese farmers using ecologic techniques significantly reduced pesticide use without expensive, patented gene-modified seeds (Yanqing 2002).

Finally, Schmidt (2005) claimed he could get no answer to his questions about industry's plans for protecting their patented seeds in the developing world. However, that answer came in 1998, when family farm advocates exposed the biotech industry's "terminator genes" that instill seed sterility in gene-altered varieties (Rural Advancement Foundation International 1998). This terminator technology was developed to ensure that farmers in the developing world could not reuse genetically engineered seed (ETC Group 2002). Advocates have uncovered over two dozen similar industry patents for seed sterility engineering (Rural Advancement Foundation International 1999). This technology threatens the lives of over 1.4 billion people who rely on saved seed for their daily nutritional needs, yet it is being brought to market by a genetic engineering industry that perversely promises to "feed the world."

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Credibility of Scientists: Industry versus Public Interest

In their article "Assessing the Reliability and Credibility of Industry Science and Scientists," Barrow and Conrad (2006) demonstrated a sophisticated understanding of the nuances of the Federal Advisory Committee Act (1972). They accurately pointed out that the act draws a distinction between conflicts of interest, which hinge on financial self-interest, and bias, which may exist for a host of reasons including research funding sources.

Alas, in their haste to condemn public interest groups who wish the government would adhere to the letter and spirit of that law, Barrow and Conrad (2006) incorrectly characterized objections by the Center for Science in the Public Interest (CSPI) and the Environmenal Working Group (EWG) to two scientists nominated in December 2004 to sit on a U.S. Environmental Protection Agency (EPA) advisory panel evaluating the risk of perfluorooctanoic acid (PFOA) (EWG and CSPI 2004). This misrepresentation may have helped prove their thesis, but it in no way reflects what is actually going on at the U.S. EPA, the National Academies, and other agencies that routinely form advisory panels.

Barrow and Conrad (2006) suggested that the CSPI and the EWG challenged two scientists because they were "funded by industry." In fact, there were nine industry-funded scientists listed as potential candidates for this panel. The two scientists singled out by the CSPI and the EWG currently or previously worked for DuPont or 3M, which have a direct financial stake in the outcome of the committee's deliberations (EWG and CSPI 2004). Thus, these scientists were covered by the conflict of interest standard, not the bias standard.

The Federal Advisory Committee Act (1972) states that scientists with conflicts of interest cannot serve on federal advisory committees unless their expertise cannot be recruited elsewhere. The EWG and CSPI (2004) suggested that there were other scientists available with the requisite expertise. The U.S. EPA must have agreed with this analysis, because the final panel announced in February 2005 (U.S. EPA 2005) did not include either scientist, although it did include two others with prior industry ties to whom the groups did not object. By contrast, only one scientist on the panel can be said to be "environmental" in orientation.

Barrow and Conrad (2006) saw this panel as proof that public interest and environmental groups are seeking to tilt the playing field against industry. In fact, industry-funded scientists often play a dominant role on committees established under the Federal Advisory Committee Act (1972). And, as in the PFOA panel case, those with financial support from industry usually outnumber by a two- or three-to-one margin those whose writings suggest they may be sympathetic to environmental or consumer interests (CSPI, in press).

Barrow and Conrad (2006) concluded that industry scientists should be allowed to serve on advisory panels because "they can provide unique knowledge and insight concerning the chemical in question." No doubt such scientists should be encouraged to present their data to a panel evaluating the health risks of a particular chemical. However, if they work full- or part-time for a company that makes, uses, or competes against the chemical, then allowing those scientists to sit on the panel would be the equivalent of allowing one side in a court case to name the jurors.

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Credibility of Scientists: Conflict of Interest and Bias

In their commentary, Barrow and Conrad (2006), both employed by the chemical industry, argued that industry-funded science and scientists are high quality and unbiased, and this is enforced through policies and practices such as disclosure of funding sources in scientific journals, guidelines for Good Laboratory Practices, peer review, the scientific process of independent repeatability, various federal laws, and the prospect of tort liability. Ironically, these same mechanisms have publicly revealed the often successful efforts by industry to weaken the regulation of their products.

The current checks and balances cited by Barrow and Conrad (2006) are not always effective guards against biased or even bad science. Numerous examples of biased industry science have been reported in the scientific literature:

- In an article co-authored by U.S. Environmental Protection Agency (EPA) scientists, Dearfield et al. (1993) compared the results from registrant-submitted mutagenicity studies to the U.S. EPA Office of Pesticide Programs with those from the published literature. The authors reported a selection bias, in which registrant-submitted studies on atrazine mutagenicity were all negative (no mutagenic activity), whereas over a dozen studies in the published literature reported mutagenic activity.
- In an analysis of studies submitted to the U.S. EPA on the effects of atrazine on frog reproductive development, Hayes (2004) reported that financial sponsorship was a strong predictor of study outcome (p = 0.009). Funding sources varied for studies reporting adverse effects (including government and industry funding), whereas all of the studies that failed to detect adverse effects were funded by the manufacturer of atrazine.
- In an analysis of 115 published studies on low-dose effects of the plastics-component bisphenol A, vom Saal and Hughes (2005) reported that > 90% of government-funded studies found significant low-dose effects, whereas none of the industry-funded studies did. More specifically, the authors found that

  > Some industry-funded studies have ignored the results of positive controls, and many studies reporting no significant effects used a strain of rat that is inappropriate for the study of estrogenic responses. (vom Saal and Hughes 2005)

- Studies of documents from the tobacco industry archives have revealed evidence of concerted industry efforts to obscure the contribution of secondhand smoke and other environmental toxics to disease

through the development of their own version of "good epidemiological practices" and "sound science" (Ong and Glantz 2001).

As Barrow and Conrad (2006) pointed out, federal scientific advisory committees and the National Academies want to include relevant experts, and therefore may appoint industry experts despite direct financial conflicts. As a solution, the International Agency for Research on Cancer (IARC) sometimes invites financially conflicted experts to speak to the committee but bars them from drafting documents or voting on evaluations (Cogliano et al. 2004). Prompt implementation of strict conflict guidelines (similar to those adopted by IARC) by the U.S. government and the National Academies should be a high priority. An editorial in The *Lancet* (2002) warned,

> Members of expert panels need to be impartial and credible, and free of partisan conflicts of interest, especially in industry links or in right-wing or religious ideology.

Barrow and Conrad (2006) argued that I am biased because my work on scientific integrity is funded by a private foundation. However, there is no financial stake in the regulation of toxics for myself, my employer, or my funders. Moreover, the funders do not review or comment on my prepublication work or influence my work product in any way. I consistently acknowledge a bias toward ensuring that regulations of toxic chemicals are as health protective as feasible, consistent with the U.S. EPA's stated goal—"to protect human health and the environment" (U.S. EPA 2005).

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Credibility of Scientists: Barrow and Conrad Respond

We appreciate Goozner's compliment that our commentary (Barrow and Conrad 2006) demonstrates "a sophisticated understanding of the nuances of the Federal Advisory Committee Act." We wish we could take credit for "accurately point[ing] out that the act draws a distinction between conflicts of interest … and bias," except that it does not—as we noted; federal rules under the Ethics in Government Act (1978) make the distinction. We did not, however, incorrectly misrepresent the Center for Science in the Public Interest's (CSPI) basis for opposing the nominations of two scientists to sit on a U.S. Environmental Protection Agency (EPA) panel. We said that the CSPI opposed them because they were "funded by industry" (Barrow and Conrad 2006). Goozner characterizes this statement as implying that the scientists were only biased, whereas in his view the scientists really "were covered by the conflict of interest standard" because they "currently or previously worked for DuPont." Alas, the scientists did not have a conflict of interest under the federal standard, which only applies to current employment or ownership (Office of Government Ethics 1997). The CSPI's own press release makes clear that one of the two scientists, an academic, "four years ago conducted 3M's $1.3-million study of … PFOA," and that the other scientist, "[p]rior to working for [his current employer], spent many years working for DuPont …." (CSPI 2004). Neither scientist worked for DuPont, or had a conflict of interest under federal rules, when he was being considered for the U.S. EPA panel.

In her letter, Sass cites four studies, involving three politically controversial chemicals, purporting to show that industry-funded research is more likely to find no adverse effects from the chemical studied, whereas government-funded studies are more likely to detect such effects. The authors of one of those studies at least recognized that these findings have two plausible interpretations: either "industry-funded scientists [are] under real or perceived pressure to find or publish only data suggesting negative outcomes," or "government-funded scientists [are] under real or perceived pressure to find or publish only data suggesting adverse outcomes …" (vom Saal and Hughes 2005). Pielke (2005) observed that such obsessive focus on funding leads journalists in particular to conclude that "research findings are 'in the eye of the beholder,'" a result he believes is "damaging to science and its role in policy."

Sass urges the U.S. government and the National Academies to adopt more stringent conflict of interest guidelines, quoting a *Lancet* (2002) editorial that actually addressed manipulation of scientific panels by politicians. In an earlier commentary, more to the point, the editor of The *Lancet* (Horton 1997) argued that financial conflicts "may not be [more] influential" than biases and that "interpretations of scientific data will always be refracted through the experiences and biases of the authors." He contended that disqualifying researchers from writing editorials or reviews because of their "associations" with industry "may harm free discussion in science." Horton (1997) concluded that "[t]he only way to minimize bias among interpretations is to allow maximum dialogue from all parties, irrespective of their interests." Making government conflict or bias rules more exclusionary will not serve that end.

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Methylmercury, Amalgams, and Children's Health

In their excellent article, Björnberg et al. (2005) stated that exposure to methylmercury in humans occurs primarily through fish consumption. We would like to make one observation about the sources of potential exposure to methylmercury in the general population.

We were surprised that Björnberg et al. (2005) failed to mention saliva as a plausible biologic source of methylmercury in individuals who have mercury dental fillings. Leistevuo et al. (2001) found a correlation between the total amalgam surfaces and organic mercury—presumably as methylmercury (CH_3Hg^+)—in saliva.

Previous studies have reported that mouth air levels of elemental mercury (Hg^0) significantly correlate with the number of occlusal surfaces (Lorscheider et al. 1995; Clarkson 2002). Hence, when mercury vapor (Hg^0) is released from amalgams and dissolved into the saliva, it exists mainly as Hg^0 and partly as inorganic divalent mercury (Hg^{2+}).

Consistent with this background, saliva has high levels of inorganic mercury associated with the total number of amalgam surfaces, which markedly increased during mastication and bruxism. In approximately 270 individuals with amalgams, we used inductively coupled plasma-mass spectrometry to measure a wide range of possible values of total mercury in saliva. Mercury levels ranged from the limit of detection [LOD; 0.1 µg/L] to 780 µg/L in both salivary baseline flow rate in unstimulated condition and in a post–chewing-gum test (Guzzi et al. 2005).

Trace amounts of elemental and inorganic mercury from saliva are taken up by oral bacteria, which in turn release methylmercury as their by-product. Heintze et al. (1983) and Lyttle et al. (1993) reported direct evidence that organic mercury in saliva is due to the transformation of bacteria. As shown in our article (Pigatto et al. 2005), the proximate cause of mercury alkylation in oral microbial communities—which occurs in dental plaque—appears to be associated with the presence of some bacteria.

Furthermore, our ongoing investigation seems to support the work of Leistevuo et al. (2001), suggesting evidence that subjects with dental amalgams have shown higher levels of methylmercury compared with controls (Guzzi et al. 2005).

Once ingested in the gastrointestinal tract, the methylmercury in saliva is therefore nearly all absorbed (> 95%), as is methylmercury in fish. Leistevuo et al. (2001) reported that the levels of methylmercury in saliva ranged from 0 to 174 nmol/L (0–37.523–µg/L), with a mean methylmercury level estimate of 14.0 nmol/L (3.019–µg/L). (Leistevuo et al. 2001). Assuming that daily adult salivary secretion is at least 800 mL, speciation analyses indicate that exposure to methylmercury through ingestion—apparently derived from oral bacteria biomethylation of inorganic mercury—is about 2–3 µg/day (Leistevuo et al. 2001). Perhaps Björnberg et al. (2005) did not deem this exposure significant?

Considering that the relevant feature of methylmercury in humans is accumulation in both adult and fetal brain, it is quite clear that, over time, the extensive exposure to methylmercury associated with dental amalgams should be taken into account. We believe that organic mercury found in saliva may indeed represent a potential nondietary source of methylmercury.

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Methylmercury, Amalgams, and Children's Health: Björnberg et al. Respond

We acknowledge the points raised by Guzzi et al. regarding our recent publication on the transport of methylmercury and inorganic mercury to the fetus and breast-fed infant (Björnberg et al. 2005). The issue is whether the methylation of inorganic mercury from dental amalgam is of sufficient size to significantly contribute to the exposure to organic mercury.

Demethylation of methylmercury into inorganic mercury is the key step in the excretion process of methylmercury. This process occurs through microbial activity within the intestine. To a limited extent demethylation may also take place in the blood (Berglund et al. 2005). The kinetics of mercury in the human body may also include methylation of inorganic mercury, but the present knowledge of this process is rather limited. Based on findings from *in vitro* studies (Heintze et al. 1983; Lyttle et al. 1993), Guzzi et al. postulate that organic mercury in saliva is due to bacterial transformation in the oral cavity. It is of course of toxicologic interest to further investigate the biotransformation of mercury in both directions.

Inorganic mercury has been shown to accumulate in exocrine glands, and saliva is also one excretion pathway for inorganic mercury (Joselow 1968). It should be pointed out that the saliva samples used by Leistevuo et al. (2001), to which Guzzi et al. refer, consist of paraffin-stimulated whole saliva. Therefore it is not possible to ascertain to what extent the sample reflects excreted mercury from the central circulation (which could originate from both inorganic mercury and methylmercury exposure) or mercury derived directly from the fillings in the oral cavity.

In the study by Leistevuo et al. (2001), 15–18% of total mercury in saliva (5–12.5 nmol/L) was organic in a group of subjects with amalgam fillings. These subjects had, on average, 22 amalgam-filled surfaces (range, 2–51). In the non-amalgam group, the organic mercury was 2–5 nmol/L. As calculated by Guzzi et al., the subjects with amalgam would ingest about 2–3 µg/day of methylmercury derived from oral bacteria biomethylation of inorganic mercury.

Our study group of pregnant women (Björnberg et al. 2005) was exposed to low levels of both methylmercury and inorganic

mercury, as reflected in the low concentrations found in blood. They consumed small amounts of fish and had few amalgam fillings, on average five amalgam-filled surfaces (range, 0–24). Therefore, the exposure to methylmercury possible originating from bacterial methylation of inorganic mercury in the oral cavity is far lower than that reported by Leistevuo et al. (2001).

It should also be pointed out that a meal of fish (200 g) containing 500 µg/kg methylmercury would result in the ingestion of 100 µg methylmercury. Also, consumption of fish with more moderate levels (50 µg/kg) would give rise to significant exposure (10 µg methylmercury).

Even though a small exposure to methylmercury may occur from bacterial methylation of inorganic mercury in the oral cavity, this exposure would be far lower than methylmercury exposure via fish consumption.

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Smoking in Pregnancy

Zanardo et al. (2005) raise an interesting issue in their article, namely, the influence of smoking on immunologic parameters and especially on the composition of human breast milk. The findings deserve notice and further investigation.

Because of the importance of the findings, the errors and inconsistencies in the article (Zanardo et al. 2005) should be corrected. The first inconsistency is related to the number of participants: In the "Materials and Methods," Zanardo et al. (2005) gave two different numbers:

> Of the 1,217 eligible participants, 25 of 26 self-identified as smokers (≥ 5 cigarettes per day through pregnancy until last trimester) were recruited for study participation. One was excluded from the final analysis because of maternal fever. Control participants included consecutive women without history of smoking and matched a smoking participant on the basis of overall inclusion criteria.

> We grouped human milk samples into third postpartum day smoker and nonsmoker mother groups, with 42 and 40 samples per group, respectively, and into 10th postpartum day smoker and nonsmoker mother groups, with 42 and 40 samples per group, respectively.

The latter numbers (42 and 40) are also repeated in the first sentence of "Results" and in Table 1. Also in Table 1 the average number of cigarettes smoked per day by the 42 smokers is given as 3.2 ± 0.7 (mean ± SD). This is inconsistent with their selection criterion of "≥ 5 cigarettes per day."

Table 1 also provides information on birth weight, gestational age, and APGAR score. As expected from numerous previous studies, the children of the smokers scored lower in all these respects. Under "statistical analysis" the authors write that they "used the Student *t*-test for the analysis of [these] data." To apply the Student *t*-test for the birth weight data seems a sensible choice. When doing this using the figures provided in Table 1, the difference of the birth weight between the children of smokers and nonsmokers is clearly highly significant ($t = 9.45$). In the "Results," Zanardo et al. (2005) stated erroneously that "the birth weight of the newborn infants of smoker mothers was not significantly lower."

The authors declare they have no financial interests.

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Reference

Zanardo V, Nicolussi S, Cavallin S, Trevisanuto D, Barbato A, Faggian D, et al. 2005. Effect of maternal smoking on breast milk interleukin-1α, β-endorphin, and leptin concentrations. Environ Health Perspect 113:1410–1413.

Editor's note: In accordance with journal policy, Zanardo et al. were asked whether they wanted to respond to this letter, but they chose not to do so.