

Substantial equivalence: Its uses and abuses

Henry I. Miller

These are trying times for biotechnology applied to agriculture and food production. Most recently, the accepted paradigms for genetically modified food risk assessment and management have come under attack from the fringes of the scientific community. These attacks have been based on the overinterpretation of experiments, flawed data, and false assumptions about risk and risk assessment. They have included the overinterpretation of a laboratory experiment that showed a modest effect on Monarch butterflies of larvae fed milkweed dusted with pollen from recombinant corn containing a *Bacillus thuringiensis* toxin¹, and a gratuitous controversy about methodologically flawed experiments by Arpad Pusztai that purportedly showed toxicity in rats fed recombinant, lectin-enhanced potatoes².

The latest attack comes in the form of a commentary by Erik Millstone et al. criticizing the application of a concept called "substantial equivalence" to the risk assessment of foods derived from recombinant DNA-manipulated organisms³. Deriding substantial equivalence as a "pseudo-scientific concept because it is a commercial and political judgment masquerading as if it were scientific," Millstone et al. appear to misunderstand the concept, its origins, and purpose. Their arguments are symptomatic of ideological opponents of the new biotechnology torturing logic and science in order to manipulate government regulation to obstruct the use of a technology that they dislike for any number of nonscientific reasons.

Millstone et al. also appear to be unaware of the prevailing regulatory standards for new foods, and of the experience with and the scientific consensus about assessing the safety of products derived through recombinant DNA techniques.

The history of the term "substantial equivalence," first applied to food by work at the Paris-based Organization for Economic Cooperation and Development

(OECD), is important. In 1986, the OECD's Group of National Experts on Safety in Biotechnology reached a consensus that

While rDNA techniques may result in the production of organisms expressing a combination of traits that are not observed in nature, genetic changes from rDNA techniques will often have inherently greater predictability compared to traditional techniques, because of the greater precision that the rDNA technique affords; [and] it is expected that any risks associated with applications of rDNA organisms may be assessed in generally the same way as those associated with non-rDNA organisms.⁴

Others echoed this consensus. In 1992, *Nature* editorialized that

... the same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods. . . [Therefore] no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes.⁵

This language was virtually identical to that in a landmark 1989 report of the US National Research Council which went even further, observing that

Recombinant DNA methodology makes it possible to introduce pieces of DNA, consisting of either single or multiple genes, that can be defined in function and even in nucleotide sequence. With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise number or the traits that have been transferred is difficult, and we cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression.⁶

This last quotation is remarkable: It expresses the widely held scientific consensus that our ability to predict "phenotypic expression," the very essence of risk-assessment related to environmental protection and public health, is *superior* for gene-spliced foods!

The OECD's experts group subsequently

took up food safety specifically, concluding in a 1993 report that

Modern biotechnology broadens the scope of the genetic changes that can be made in food organisms, and broadens the scope of possible sources of foods. This does not inherently lead to foods that are less safe than those developed by conventional techniques. Therefore, evaluation of foods and food components obtained from organisms developed by the application of the newer techniques does not necessitate a fundamental change in established principles, nor does it require a different standard of safety.⁷

In that same report, the group described the concept of substantial equivalence in new foods not, as asserted by Millstone et al., as a scientific principle, but merely as a kind of regulatory shorthand for defining those new foods that do not raise safety issues that require special, intensive, case by case scrutiny. (The appropriation of the concept and the name—both borrowed from the US Food and Drug Administration's (FDA) definition of a class of new medical devices that do not differ materially from their predecessors, and thus, do not raise new regulatory concerns—was suggested by a member of the OECD experts group, senior US White House adviser John J. Cofresen.)

The OECD has continued to explore the concept of substantial equivalence, another expert group concluding in 1998 that

While establishment of substantial equivalence is not a safety evaluation per se, when substantial equivalence is established between a new food and the conventional comparator [i.e., an antecedent], it establishes the safety of the new food relative to an existing food and no further safety consideration is needed.⁸

It bears repeating that substantial equivalence is not intended to be a scientific formulation; it is a conceptual tool for food producers and government regulators, and it neither specifies nor limits the kind or amount of testing needed for new foods.

The FDA's 1992 policy on foods from "new plant varieties" is instructive in this regard, because although the agency does not formally use the term, it applies the concept in its risk-based, scientifically defensible approach⁹. This policy applies irrespective of whether the plant arose by gene-splicing or "conventional" genetic

Henry I. Miller is a senior research fellow at the Hoover Institution, Stanford University, Stanford, CA 94305-6010, miller@hoover.stanford.edu. He was founding director of the US Food and Drug Administration's Office of Biotechnology, 1989-93 and a member of the OECD Group of Experts on Safety in Biotechnology, 1984-92.

engineering methods. The FDA does not routinely subject foods from new plant varieties to premarket review or to extensive scientific safety tests. Instead, it considers that the usual safety and quality control practices used by plant breeders—mostly chemical and visual analyses and taste testing—are generally adequate for ensuring food safety.

The FDA's policy defines certain safety-related characteristics of new foods that, if present, require greater scrutiny by the agency. These include the presence of a substance that is completely new to the food supply, an allergen presented in an unusual or unexpected way (for example, a peanut protein transferred to a potato), changes in the levels of major dietary nutrients, and increased levels of toxins normally found in foods. Additional tests are performed when suggested by the product's composition, characteristics or history of use. For example, potatoes are generally tested for the glycoalkaloid solanine, because this natural toxin has been detected at harmful levels in some new potato varieties that were developed with *conventional* genetic techniques.

The absence of such characteristics that are correlated with enhanced risk in effect defines foods that are substantially equivalent to antecedent products. Foods lacking characteristics that raise these safety issues are not subjected to premarket FDA review.

By considering all recombinant DNA-mediated genetic changes—but only those—as novel, Millstone et al. are inconsistent.

They seem unimpressed by the fact that thousands of foods containing gene-spliced ingredients have for years been consumed routinely and safely by consumers in Europe and North America. Likewise, they ignore the fact that many products on the market are derived from “wide crosses,” hybridizations in which genes are moved from one species or one genus to another to create a variety of plant that does not and cannot exist in nature. They demand extensive, difficult to perform, hugely expensive “biological, toxicological and immunological”³ testing of foods from recombinant plants, but not of other foods from the dozens of new plant varieties improved with far less precise traditional techniques of genetic modification, such as hybridization, that enter the marketplace each year without premarket review or special labeling.

But the testing of fundamentally benign whole foods—gene-spliced or not—in animal feeding studies, for example, is limited by factors such as the animal's qualitative and quantitative feeding preferences, and by the levels of nutritional and non-nutritional substances that are present in the food under study. When Harry Kuiper of the State

Institute for Quality Control of Agricultural Products in Wageningen, The Netherlands, attempted to determine the toxic threshold for a recombinant tomato by feeding rats freeze-dried tomato extract, the experiments were limited to the equivalent of 13 tomatoes a day because of the negative effects of naturally occurring inorganic compounds such as potassium in the tomato powder. But, as noted by Kuiper, “toxicologists still said we hadn't fed them enough to get a meaningful result.”¹⁰

Wholly ignoring such empirical experience, as well as scientific consensus, Millstone et al. suggest that gene-spliced food should be treated “in the same way as novel chemical compounds, such as pharmaceuticals, pesticides and food additives,

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and [requiring] a range of toxicological tests, the evidence from which could be used to set acceptable daily intakes (ADIs).³ Then, of course, we would need “regulations . . . to ensure that ADIs are never, or rarely, exceeded.”³

This sort of argument illustrates the fallacy that underlies many of the unscientific attacks on the new biotechnology—the assumption that somehow gene-splicing systematically introduces into organisms (and the foods derived from them) greater uncertainty or risk than other, older, less precise techniques. As described above, neither scientific consensus nor empirical evidence supports that view.

If new and Draconian regulatory regimens are appropriate for the new gene-splicing biotech, they are certainly also applicable to the old traditional biotech. In that regard, one must wonder how we would calculate the ADI for the mutant peach called a nectarine, or the tangerine-grapefruit hybrid called a tangelo. Such an exercise would clearly be absurd. And where it is not absurd—such as when estimating the acceptable intake of foods known to have high endogenous levels of solanine, such as potatoes—the exercise has nothing to do with the method of genetic manipulation used to construct the plant.

A central theme of Millstone et al.³ is that the widespread endorsement and use of substantial equivalence is, in effect, the result of a conspiracy by industry and government to avoid the adequate testing of foods from recombinant organisms. Not only are they inaccurate in suggesting that the testing of the foods themselves is deficient, but they have completely ignored the quality assurance that is part of the certification of plant seeds sold to agricultural producers or growers, in order to prevent any compromise of seed quality or consistency.

In California, for example, oversight is performed by the non-profit California Crop Improvement Association (CCIA), which provides a voluntary quality assurance program for the maintenance and increase of crop seed. (CCIA is the designated California authority for the international seed certification scheme administered by OECD in 40 countries.) Each variety that enters this program is evaluated for its unique characteristics such as pest resistance, adaptability, uniformity, quality and yield.

Seed production is closely monitored by CCIA to prevent outcrossing, weed, and other crop and disease contamination that may negatively affect seed quality. Seed movement is monitored from field harvest, through the conditioning plant, and into the bag. Samples can be rejected if “off-type” seeds are found at a percentage that is greater than standards permit, as is occasionally the case with beans, cereals, and sunflowers.

Healthy skepticism is necessary for the evolution of scientific thought and discussion, to be sure, but so are consistency and the application of accurate assumptions, and of late we have seen far too little of these latter elements in the debates about the new biotechnology used for agriculture and food production. Discussions of public policy, like those about science, cannot tolerate those who take lightly the moral obligation to report strictly what is true, and in the proper context. Everyone must be held to that standard.

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