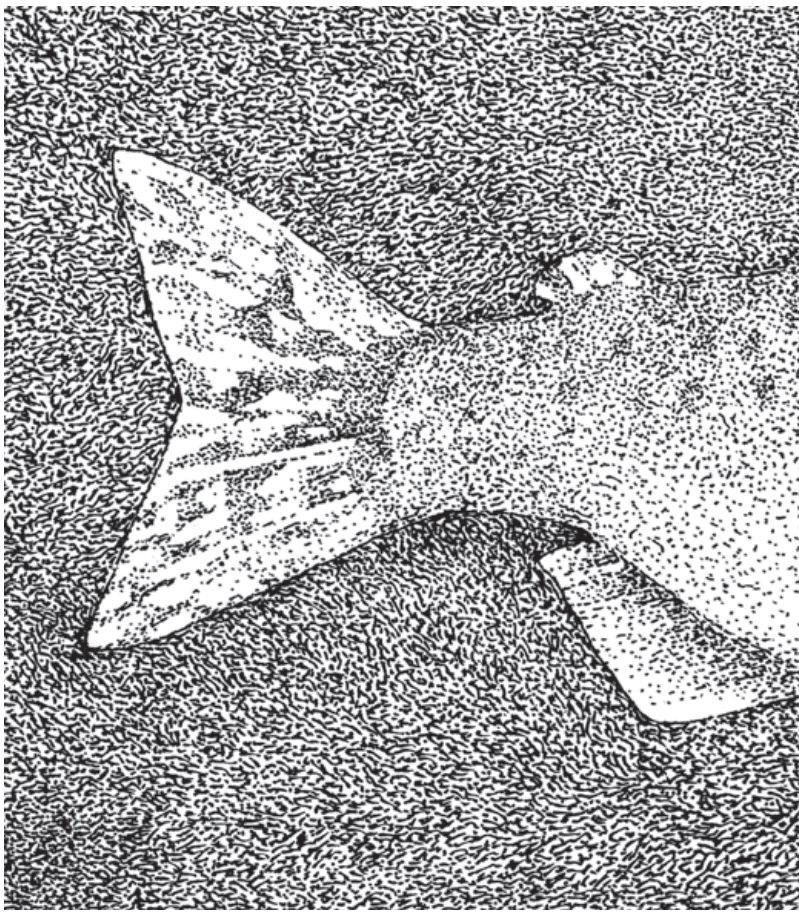
The Use and Abuse of Science in Policymaking

The regulation of biotechnology provides a cautionary tale of politicized science.

BY HENRY I. MILLER

The modern techniques of genetic engineering—also known as biotechnology, recombinant DNA technology, or genetic modification—offer plant breeders the tools to make old crop plants do spectacular new things. In the United States and two dozen other countries, farmers are using genetically engineered crop varieties to produce higher yields with lower inputs and reduced environmental impact. Most of these new varieties are designed to be resistant to pests and diseases that ravage crops or to be resistant to herbicides so that farmers can more effectively control weeds while adopting more environment-friendly no-till farming practices and more benign herbicides. Other varieties possess improved nutritional quality. But the greatest boon of all in the long term, both to food security and the environment, may be the ability of new crop varieties to tolerate periods of drought and other water-related stresses.

In spite of such benefits, many of which have already been realized, and the absence of adverse effects, these advances are opposed staunchly by anti-biotechnology activists. Their intractable opposition and outright lies about supposed adverse impacts of genetically engineered plants—ranging from claims of allergic reactions to allegations of killing butterflies and bees—have led to public confusion and government over-regulation. Over the last few years, four California counties have gone so far as to ban the cultivation or sale of genetically engineered plants, including



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those that could help to ameliorate critical local and regional pest infestations and shortages of water. As recently as March 2012, a coalition of anti-biotechnology nongovernmental organizations claimed to have amassed more than a half-million signatures on petitions calling for mandatory labeling of foods made from genetically engineered organisms.

Baseless charges may confuse not only the public, but also policymakers. Donald Kennedy, president emeritus of Stanford University and former head of the U.S. Food and Drug Administration, chided bureaucrats: "Frequently decisionmakers give up the difficult task of finding out where the weight of scientific opinion lies, and instead attach equal value to each side in an effort to approximate fairness. In this way extraordinary opinions ... are promoted to a form of respectability that approaches equal status."

This kind of undeserved moral equivalence frequently compromises governmental decisionmaking. It has given rise to unscientific and inconsistent regulation of not only biotechnology applied to agriculture but also many other products and technologies, including pesticides and other chemicals and silicone breast implants.

In addition to undeserved moral equivalence, we have the problem of a kind of moral relativism applied to science itself. During the Clinton administration, then–under secretary of agriculture Ellen Haas, who previously headed an anti-technology advocacy group, deconstructed science thus: "You can have 'your' science or 'my' science or 'somebody else's' science. By nature, there is going to be a difference." Translation: "I don't care about the consensus in the scientific community. My views are just as valid."

In the remainder of this article, I will review the government regulation of genetically engineered plants and fish as case studies of scientific consensus completely ignored or perverted in the formulation of regulatory policy.

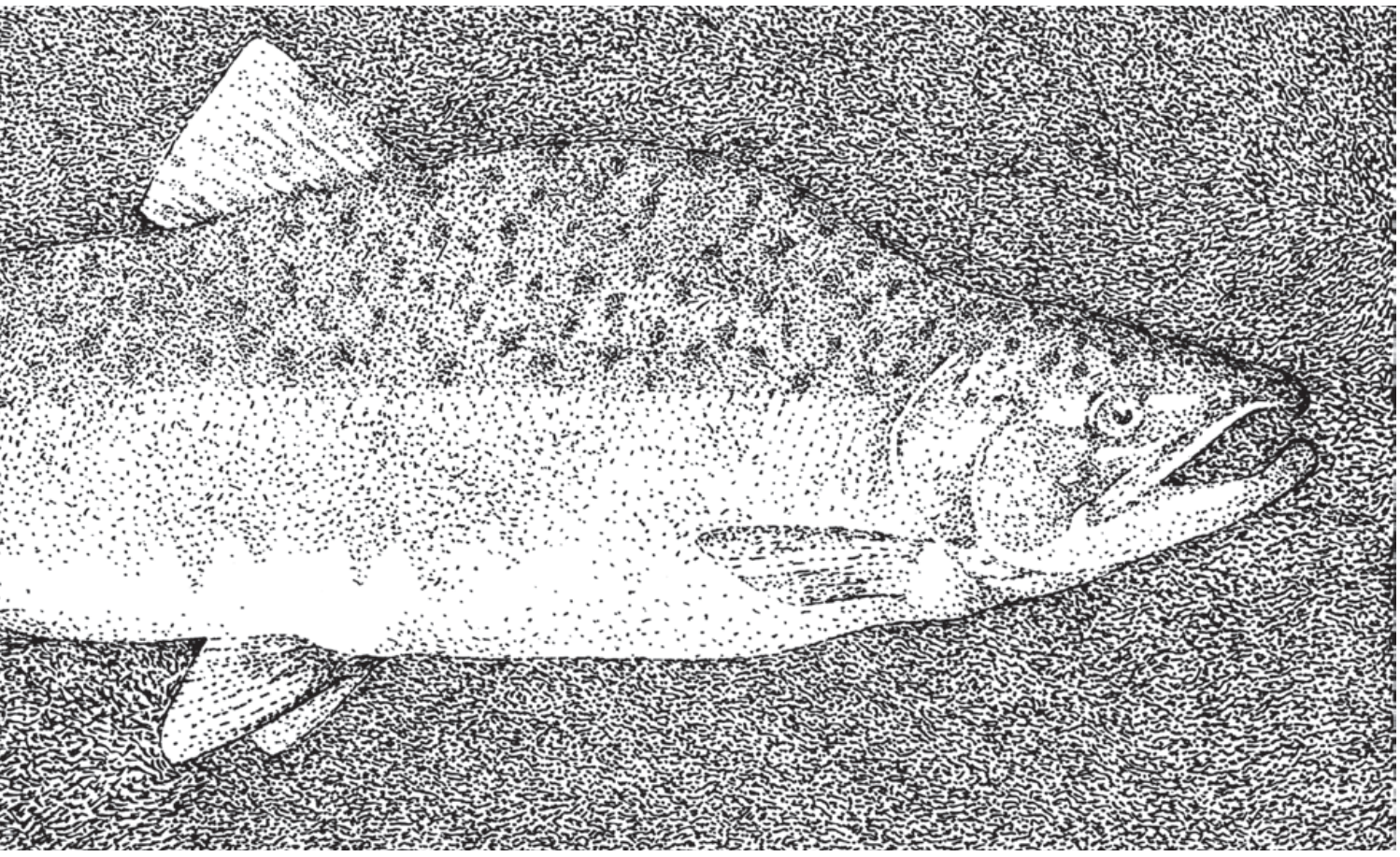
Genetically Engineered Plants

Based on empirical data and scientific principles, the scientific consensus about the nature of genetic engineering has long been unequivocal. It holds that risk is primarily a function of the characteristics of a product—whether that product is an intact organism or something derived from it—and that the risk is not a function of the method of genetic modification (if any) per se. That consensus, the critical elements of which are discussed below, has been bolstered by many national and international groups, repeatedly and in remarkably congruent terms over three decades.

As long ago as 1982, an analysis performed by the World Health Organization Regional Office for Europe concluded that "genetic modification is not new" and "risks can be assessed and managed with current risk assessment strategies and control methods." Recall that "current" referred to 1982.

Over many millennia, there has been a virtually seamless continuum of genetic improvement of crops using increas-

ILLUSTRATION BY MORGAN BALLARD



ingly sophisticated techniques. Recombinant DNA modification, a more precise scientific term I will use interchangeably with "genetic engineering," was introduced during the 1970s as part of this progression of technologies. Thus, because genetic modification, or improvement, has been with us for centuries, the term "genetically modified organism" and its abbreviation "GMO"—commonly used nomenclature—are unfortunate choices of terminology. "GMO" is often used arbitrarily to mean organisms containing genes transferred across species lines only when accomplished by recombinant DNA, or "gene-splicing," techniques. But this usage ignores the fact that genetic modification can be achieved using many technologies and that recombinant organisms are not in any way a meaningful "category." The then-head of the FDA, Frank Young, and I co-authored a *Wall Street Journal* commentary on this subject, "Biotechnology: A Scientific Term in Name Only," on January 13, 1987.

For example, innumerable new genetic variants of plants field-tested each year are derived from "wide-cross hybridizations" in which genes have been moved across species or genus barriers by techniques that are more than a half-century old. Thousands of such "non-molecular genetically modified varieties" (as they might be called) are in commerce around the world. Examples include corn, tomatoes, pumpkin, oats, and black currants.

Most agricultural crops are the products of hundreds if not thousands of years of genetic improvement. Corn, for example, has undergone gradual but drastic modification that has seen it evolve from the original grass-like plant *teosinte*, with primitive, meager kernels, into modern varieties with regularly arranged kernels replete with carbohydrate, oil, and protein. Yet no one seems to consider corn "unnatural."

A more recent example of the irrationality of current conceptions of "natural" versus "genetically engineered" is a potential medical miracle called Golden Rice, whose name derives from the yellow color of the grains that comes from its biofortification with beta-carotene, the precursor of Vitamin A. The genetic pedigree of the immediate precursor of Golden Rice, IR64, a strain of rice widely used in many parts of the world, shows that it has been modified in dozens of ways by several genetic techniques. The conversion of IR64 to Golden Rice was accomplished by recombinant DNA techniques with the insertion of two genes, one each from rice and corn.

What is astonishing about this construction is that, for regulatory purposes, all of the complex genetic changes—including mutations, recombinations, deletions, and translocations—that led from some primitive genome to IR64 are somehow considered not to constitute genetic engineering, but to be "natural." They elicit no attention from the public or regulators. But the precise insertion into the genome of two well-characterized, harmless genes that enable the plant to synthesize beta-carotene (which is converted to Vitamin A in vivo) precipitates a monumental burden of regulatory costs and delays for Golden Rice. This dichotomy defies rational explanation.

In almost every regulatory regime around the world, the use of recombinant DNA techniques is the trigger for draconian, dilatory, and expensive regulatory regimes. The commercialization of Golden Rice, which could save hundreds of thousands of lives annually, has been delayed by regulatory red tape for more than 10 years. Arguably, it is a product that, like other new corn varieties, warrants no regulatory review at all.

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The Scientific Basis of Regulation

The very basic and—to anyone who understood the science—almost tautological observations from the 1982 WHO group were echoed and expanded in a 1987 white paper from the U.S. National Academy of Sciences (NAS) that observed that recombinant DNA techniques offer a powerful and safe means for modifying organisms. The paper predicted that the technology would contribute substantially to improved health care, agricultural efficiency, and the amelioration of many pressing environmental problems. Its most significant conclusions and recommendations include:

- There is no evidence of the existence of unique hazards either in the use of recombinant DNA techniques or in the movement of genes between unrelated organisms.
- The risks associated with the introduction of recombinant DNA–modified organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods.
- Assessment of the risks of introducing recombinant DNA–modified organisms into the environment should be based on the nature of the organism and of the environment into which the organism is to be introduced, and independent of the method of engineering per se.

In a 1989 follow-up to that white paper, the National Research Council (NRC), the research arm of the National Academy of Sciences, commissioned academic experts to perform another extensive analysis to extend the earlier observations. "The committees [of experts commissioned by the NRC] were guided by the conclusion (NAS, 1987) that the product of genetic modification and selection should be the primary focus for making decisions about

the environmental introduction of a plant or microorganism and not the process by which the products were obtained."

According to the 1989 NRC report:

- No conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes.
- Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits. Because the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants.
- The types of modifications that have been seen or anticipated with molecular techniques are similar to those that have been produced with classical techniques. No new or inherently differently hazards are associated with the molecular techniques. Therefore, any oversight of field tests should be based on the plant's phenotype and genotype, and not on how it was produced.
- The same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods.
- 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. However, predicting the precise number or the traits that have been transferred is difficult and science cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods, science is in a better, if not perfect, position to predict the phenotypic expression.
- With classical methods of mutagenesis, chemical mutagens such as alkylating agents modify DNA in essentially random ways. It is not possible to direct a mutation to specific genes, much less to specific sites within a gene. Indeed, one common alkylating agent alters a number of different genes simultaneously. These mutations can go unnoticed unless they produce phenotypic changes that make them detectable in their environments. Many mutations go undetected until the organisms are grown under conditions that support expression of the mutation.
- Information about the process used to produce a genetically modified organism is important in understanding the characteristics of the product. However, the nature of the process is not a useful criterion for determining whether the product requires less or more oversight.
- The product of genetic modification and selection should be the primary focus for making decisions about the environmental introduction of a plant or microorganism and not the process by which the products were obtained.
- Established confinement options are as applicable to field introductions of plants modified by molecular and cellular methods as they are for plants modified by classical genetic methods.

The NRC experts posited that the evaluation of experimental field testing should be based on three considerations:

- familiarity, i.e., the sum total of knowledge about the traits of the organism and the test environment;
- the ability to confine or control the spread of the organism, as necessary; and
- the likelihood of harmful effects if the organism should escape control or confinement.

Thus, the NRC articulated some of the principles and concepts that should underlie the regulatory oversight of field trials. Subsequently these principles have been reiterated repeatedly by countless scientific bodies worldwide. The essence of these is that the mere fact that an organism has been modified by recombinant DNA genetic engineering techniques should not determine how the organism is regulated.

Echoing and extending earlier analyses, a 1992 report of the National Biotechnology Policy Board concluded:

> The risks associated with biotechnology are not unique, and tend to be associated with particular products and their applications, not with the production process or the technology per se. In fact, biotechnology processes tend to reduce risks because they are more precise and predictable. The health and environmental risks of not pursuing biotechnology-based solutions to the nation's problems are likely to be greater than the risks of going forward.

Principles of Regulation

In addition to conforming to the consensus described above specifically for the products of genetic engineering, there are certain general principles that should inform any regulatory scheme:

- The degree of regulatory scrutiny should be commensurate with the perceived level of risk.
- Similar things should be regulated in a similar way.
- The scope of what requires regulatory review must make sense. If the scope of regulation—i.e., the regulatory net or the trigger that circumscribes which field trials or finished products are subject to regulatory review—is unscientific, then the entire approach is unscientific.

At least in theory, these academically articulated principles were embraced by federal policymakers. On June 26, 1986, the White House Office of Science and Technology Policy published a policy statement called "The Coordinated Framework for the Regulation of Biotechnology." The statement called for oversight and regulatory triggers to focus on the risk-related characteristics of products, such as plants' weediness or toxic-

ity, rather than on the process used for genetic modification.

This approach was reaffirmed in a 1992 policy statement on the appropriate "scope" of regulation that set forth the overarching principle that the degree and intrusiveness of oversight "should be based on the risk posed by the introduction and should not turn on the fact that an organism has been modified by a particular process or technique." This reflected the broad consensus in the scientific community that the newest techniques of genetic modification were essentially an extension, or refinement, of older, less precise, and less predictable ones.

Science Spurned

But the Environmental Protection Agency and U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) were swayed by neither the consensus of the scientific community nor the directives from the White House. Nor was there sufficient commitment or power exerted by White House organizations—including the regulatory side of the White House Office of Management and Budget, the Domestic Policy Council, or the Office of Science and Technology Policy—that should have been able to affect policy outcomes.

The policymakers in the agencies knew that they could outlast and outmaneuver their political bosses. They were bent on creating new bureaucratic regulatory empires—with or without scientific justification—and create them they did. They were abetted by a handful of know-nothing congressional ideologues (both members and staffers) and, perhaps most important of all, by several powerful agribusiness companies that regarded excessive, expansive regulation as a convenient market-entry barrier to competitors. The media's consistently lending exaggerated credibility and ink to the alarmist claims of anti-biotech activists provided further cover. (Keith Schneider, then the *New York Times*' national environmental affairs reporter, was a serial offender.) The resulting stultifying regulation has inhibited research and development, particularly in public institutions, ever since.

In 2001, the EPA concocted a new concept called "plant-incorporated protectants," defined as "pesticidal substances produced and used by living plants." But the agency applied its regulatory jurisdiction only if the "protectant" was introduced or enhanced by recombinant DNA technology, the most precise and predictable techniques of genetic engineering. The EPA's approach thus ignores any consideration of actual risk to human health or the natural environment. The sale of these plants requires that sponsors go through the same process that applies to the licensing of toxic chemical pesticides, which demands copious data on the parental plant, the genetic construction, the behavior of the test plant, and so on—data requirements that could not be met for any plant modified with older, cruder techniques (which are exempt). Under a different statute, the EPA crafted equally unsatisfactory and scientifically insupportable rules for microorganisms.

The USDA has been no better. APHIS had long regulated the importation and interstate movement of plants and plant products that are pests, which were defined by means of an inclusive list. This approach is essentially binary—"thumbs up or thumbs down." A plant that an investigator might wish to introduce into the field is either on the prohibited list of plants pests—and therefore requires a permit—or it is exempt. This straightforward approach is risk-based in that the organisms required to undergo case-by-case governmental review are an enhanced-risk group—organisms that can injure or damage plants—compared to plants not considered to be plant pests.

But this risk-based USDA regulation has an evil twin. For the past two decades, the USDA has maintained a parallel regime focused exclusively on plants altered or produced through recombinant DNA technology. The scope of what is regulated is essentially independent of risk. The USDA tortured the original concept of a plant pest as something known to be harmful and crafted a new, jury-rigged category: a "regulated article," defined in a way that captures essentially every recombinant DNA–modified plant for case-by-case review, regardless of its potential risk.

In order to perform a field trial with a regulated article, a researcher must apply to the USDA for permits at every stage of development and submit a huge amount of data, which makes genetically engineered plants extraordinarily expensive to test and commercialize.

This approach to regulation makes no sense. Plants have long been selected by nature and bred by humans or irradiated to create mutants with enhanced resistance or tolerance to external threats to their survival and productivity. These threats include insect predation, disease organisms, herbicides, and environmental stresses. Indeed, all plants contain resistance traits or they would not survive. Pest resistance and other traits related to yield or other desired qualities have thus been introduced and enhanced for centuries by a variety of genetic modification techniques. So, for example, primitive wheat breeders crafted durum (hard) wheat for pasta and softer wheat varieties for cakes, and numerous varieties of corn and tomatoes have been bred for various purposes and microclimates.

Plant breeders have learned from experience about the need for risk analysis, assessment, and management. New varieties of plants that normally harbor relatively high levels of toxins—such as celery, squash, and potatoes—are analyzed carefully to make sure that levels of potentially harmful substances remain in the safe range (whatever techniques are used to craft them). Consequently, in spite of the many thousands of genetic improvements plant breeders have introduced, only a handful of plants produced have manifested any significant hazards for the environment, human health, or food safety. And all of those hazardous plants were crafted with older, unregulated genetic modification techniques.

Consequences | The principles of regulation described above have been largely ignored. Current regulatory regimes are unscientific, technique-based, and require case-by-case review for virtually all genetically engineered plants and microorganisms, no matter how obviously trivial the modification or benign the

product might be. This flawed approach, which categorically ignores fundamental principles of regulation and the dictates of common sense, results in enormously inflated costs, lack of agricultural progress, and human suffering.

The compliance costs of regulation for the development of an insect-resistant and an herbicide-resistant variety of corn have been calculated to be $6 million and $15 million respectively, not including labeling. This is several times more costly than for similar constructions made with conventional breeding, in spite of the latter being less precise and predictable and often less effective. The costs and uncertainty created by unscientific regulation have impaired agricultural innovation and product development, inhibited the commercialization of already-developed genetically engineered crops, and decreased the potential for new, improved varieties of "specialty crops" such as fruits and vegetables, tree fruits and nuts, and nursery and landscape crops.

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The bottom line is that unscientific and excessive regulation has made development economically viable primarily for commodity crops, which are grown at vast scale. As Gregory D. Graff, Gal Hochman, and David Zilberman wrote in a 2009 paper appearing in *AgBioForum*:

> The resulting regulatory environment has delayed and eliminated the introduction of many new technologies and products.... Foregone benefits from these otherwise feasible production technologies are irreversible.

A Little Over-Regulation Goes a Long Way

Pseudo-crises—false alarms propagated by activists about dangers from genetically engineered products—have led to public relations debacles, flawed public policy, costly court trials, and endless debate over issues such as the feasibility of "coexistence" of genetically engineered and conventional crops, mandatory labeling, and acceptable tolerances for "contamination." One well-known example of government and industry falling prey to the Law of Unintended Consequences is the StarLink corn case in which the EPA gave "split," or partial, approval of a genetically engineered corn variety, sanctioning it for animal but not human consumption. After it was subsequently detected in human foodstuffs, the regulatory and civil penalties for the developer of StarLink were substantial even though the corn was perfectly safe for human consumption and not a single person suffered any adverse effects.

The USDA's regulatory approach, which requires review and approval of virtually all field trials and commercial sale of recombinant DNA–modified organisms, has created a legal quagmire. Under the National Environmental Policy Act of 1969 (NEPA), federal government agencies are required to consider the effects that any "major actions" they take may have on the "human environment." The obligation is triggered by all manner of decisions, such as the proposal of a new regulation, a plan for a new federally funded highway, or "deregulating" (that is, approving) a new variety of recombinant DNA–modified plant.

Federal court decisions in 2006 and 2007 resulted in the revocation of field trial permits to test several different genetically engineered varieties, establishing the precedent that nearly any cultivation of a new genetically engineered plant would require a complete Environmental Impact Statement. Two additional lawsuits filed to stop the approval and commercial sale of genetically engineered alfalfa and sugar beet varieties have been a nightmare for plant breeders, the seed industry, and especially farmers. Ironically, in none of those cases was there any actual environmental harm from the crop varieties in question—quite the opposite, in fact. Other pseudo-crises include the false alarms over killing of Monarch butterflies and contamination of land races in Mexico as the result of horizontal gene transfer from recombinant DNA–modified corn plants. All of these crises arose from inaccurate or fraudulent reports or results taken out of proper context.

Field trials are constantly being vandalized because in many places the regulatory requirements, which are specific to and discriminate against recombinant DNA–modified products, dictate that the sites of trials become publicly known. (This is another disadvantage of declaring genetic engineering a regulated "category.") Researchers have been injured, research destroyed, and in Germany two universities responded to activists' threats by banning the testing of recombinant DNA–modified plants, an appalling example of cowardice and abdication of academic freedom.

A (Genetically Engineered) Fish Story

Biotechnology's regulatory and political travails are not limited to applications to agriculture.

"Bringing home the pork" is an old and venerable tradition in the U.S. Congress; elected officials need to please their constituents, after all. But when politicians substitute absurd fantasies or dissembling for scientific evidence, parochial concerns can go beyond what is ethical or in the public interest. An example is the demand in July 2011 by several members of both houses of Congress that the FDA stop doing some of the very work the

agency is empowered to do on behalf of American consumers: regulate food safety.

The legislators' letter to the FDA follows legislation passed by the House in June 2011—an amendment to an FDA (and other agencies) appropriations bill by Reps. Don Young (R, Alaska) and Lynn Woolsey (D, Calif.)—that bars the agency from expending funds to approve a genetically engineered salmon, regardless of the agency's unprecedentedly thorough and unequivocal scientific and environmental review. Senators threatened similar legislation but, as of March 2012, had not followed through.

The congressional rationale? "Given the strong and growing congressional opposition to the approval of [genetically engineered] fish in both chambers, spending time on further review of [genetically engineered] fish would be a waste of taxpayer dollars." But the real waste of taxpayer dollars is congressional interference just as the (overly) extensive and expensive regulatory process appeared to be nearing the end. Why would West Coast lawmakers suddenly become so concerned about saving taxpayer money in this way? Perhaps because the genetically engineered fish, known as the AquAdvantage salmon and engineered to grow quickly in fish farms, posed a competitive threat to the incumbent salmon fishing industry. This is crony capitalism and malfeasance at its worst, tantamount to legislators from New Jersey organizing an effort to block approval of a superior new medicine made in California because it would pose an economic threat to a drug made by a New Jersey-based pharmaceutical company.

What makes the congressional actions particularly insupportable and reprehensible is that the FDA's process itself was already excessively burdensome. After more than a decade of dithering, in 2008 the FDA's Center for Veterinary Medicine decided that every genetically engineered animal intended for food would be subjected to the same pre-market approval procedures and regulations as drugs such as pain relievers and anti-flea medicines used to treat animal diseases. The rationale is that a genetically engineered construct "that is in a [genetically engineered] animal and is intended to affect the animal's structure or function meets the definition of an animal drug." But this explanation conveniently ignores the science, the FDA's own precedents, and the availability of other, more appropriate regulatory options. Adoption of the FDA's existing approach to foods (which is far less lengthy and intensive than that for veterinary drugs) would have sufficed and should have been applied to genetically engineered animals intended for consumption. But characteristically, regulators tortured the regulations to invoke the most risk-averse and burdensome approach.

Genetic engineering of food products is, in fact, old hat. Except for wild game, wild mushrooms, wild berries, and fish and shellfish, virtually all the food in European and American diets has long been derived from genetically modified organisms—even the organic stuff at Whole Foods and the local farmers' market. Tangelos resulted from a genetic cross between tangerines and grapefruit, for example. Yogurt, beer, tofu, and bread are made with microorganisms that have been painstakingly modified and optimized over centuries. Grains, in particular, have been intensively engineered over millennia for higher yields, pest- and disease-resistance, and various other desirable characteristics. For example, although modern wheat varieties vary widely in their traits and genetics, all are derived from a common precursor first domesticated in Turkey around 9,000 B.C. and subsequently genetically improved by farmers, plant breeders, and biologists. Current varieties include durum wheat for pasta and so-called common wheat for bread.

Animals, too, have been genetically engineered, mostly by laborious and imprecise trial-and-error breeding techniques. The dozens of varieties of cattle raised today are all derived from the now-extinct auroch, which was used both for food and as a beast of burden from ancient times until the 17th century. A relatively recent new food animal, the "beefalo," a cow-bison hybrid, combines the superior hardiness, foraging ability, ease of calving, and low-fat meat of the bison with the fertility, milking ability, and docility of the cow.

Moreover, echoing the dysfunctional regulatory approach of the EPA and USDA described above, the FDA's onerous pre-marketing approval requirements apply only if the animal has been modified with state-of-the-art recombinant DNA techniques. Thus, if the fast-maturing Atlantic salmon described above were the result of some sort of artificial insemination or irradiation instead of the highly precise genetic engineering techniques that were used, it would be exempt from pre-approval evaluation. That is also true for food animals long produced with less precise, less predictable methods of genetic modification, such as the beefalo, which has never been regulated by the FDA. In other words, the trigger for the FDA's review is not the risk-related traits of an animal, but the use of a certain technology—and the most precise and predictable one at that. That makes no sense.

Even before Congress's 11th-hour interference, the FDA's policy resulted in an entire innovative business sector burdened with a policy that inflates research and development costs, inhibits innovation, and deprives consumers of health-promoting and less-expensive products. Not surprisingly, very few companies are willing to swim upstream against such a powerful regulatory current.

The poor AquAdvantage fish that has been treading water in regulatory limbo for more than a decade is simply an Atlantic salmon that contains a Chinook salmon growth hormone gene; that gene is turned on all year long instead of only during the warmer months, as in nature. This roughly halves the salmon's time to reach a marketable adult weight. The genetic change confers no detectable difference in its appearance, ultimate size, taste, or nutritional value. It just grows faster, which is a tremendous economic advantage to those farming the fish in a closed water system. It is also an advantage to consumers, who will be able to take advantage of greater supply and lower prices. Lower-priced salmon would be a boon for consumers seeking low-fat and affordable options for protein sources, especially in the face of food price inflation and the obesity epidemic.

The FDA's exhaustive analysis concluded that the salmon has no detectable differences and that it "is as safe as food from conventional Atlantic salmon." And because the fish will all be

sterile females and farmed inland, there is negligible possibility of any sort of "genetic contamination" of the gene pool or other environmental effects. (Even in a worst-case scenario, these fish would compete poorly in the wild.)

This saga gets worse and worse. Had the FDA selected the most appropriate paradigm, the AquAdvantage salmon would have been deemed "Generally Recognized As Safe" and no review by the FDA would have been required at all. But the FDA decided to review—seemingly interminably—the fish as though it were (or contained) an animal drug. And after the FDA had finally decided that the "drug" was safe and effective, the final decision was hijacked by Congress and the White House, where it remains in limbo. This has been a disgrace at every level; and as discussed below, that's not all.

Even a decade-plus of review and dithering was not enough for Sen. Mark Begich (R, Alaska), whose home-state salmon industry would be a prime beneficiary of a decision to block the more efficient fast-growing salmon. He alleged that the "FDA hasn't considered all of the potential negative impacts of genetically altered fish and the strong opposition in Congress to approving something that could decimate wild salmon populations." Rubbish.

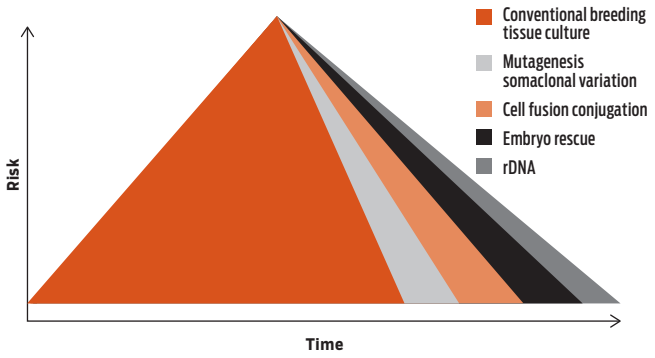
In this fish story, an innovative new product that could be highly beneficial to society has confronted a perfect storm: empire-building by regulators, naiveté from industry, disingenuous opposition from activists, and malfeasance by legislators. It now faces preposterous, discriminatory regulatory obstacles so that consumers will pay inflated prices for scarcer (and often inferior-quality) goods.

Officials at AquaBounty, the company that created the fast-growing salmon, initially embraced the FDA's more burdensome review pathway, but they have (at last) become disillusioned. Ronald Stotish, the company's chief executive officer, lamented:

> We hoped that the rigorous science-based review would provide confidence and assurance to the general public that their interests were being protected.... In retrospect, however, we were naive to assume that the well-organized and well-funded opponents of technology would accept a science-based process. The environmental and organic lobbies ignored the data and the FDA conclusions, and proceeded with their attacks. In my personal view, the "transparency" exercise in political correctness simply provided opponents an opportunity to crucify the company, the FDA, and the science-based process.

FIGURE 1

Distribution of Risk in Field Trials



Stotish's statement could be the eloquent epitaph for a once-promising industrial sector. Other innovators who might be tempted to invest in or create new technologies and products will get the message: even with a superior product, you can be blindsided by cynical and perfidious political forces as you near the finish line. The development of promising transgenic animals would then follow into oblivion other sectors once touted as potential sources of breakthroughs, including biofortified crops and microorganisms for bioremediation and used as biorational pesticides.

Risk-Based Approaches to Biotechnology Regulation

There are better alternatives to the current unscientific, non-risk-based regulation of genetic engineering, and science shows the way. One that is directly applicable to biotechnology products and that has been enshrined in federal regulations for two decades is the FDA's approach to "novel" foods. Published in 1992, it emphasizes that the agency's Center for Food Safety and Nutrition does not impose discriminatory regulation based on the use of one technique or another, and that greater scrutiny is applied only when certain safety issues are raised. Those safety issues include the presence of a completely new substance in the food supply, changes in a macronutrient, an increase in a natural toxicant, or the presence of an allergen where a consumer would not expect it.

Stanford Model | Another alternative, which could easily be applied to the oversight of field trials and the commercialization of genetically engineered plants and other organisms, is the "Stanford Model" for risk-based regulation. More than a decade ago, the Stanford University Project on Regulation of Agricultural Introductions developed a widely applicable regulatory model for the field-testing of any organism, whatever the method or methods employed in its construction.

The approach is patterned after quarantine systems such as the USDA's Plant Pest Act regulations, which are essentially binary: a plant that a researcher might wish to introduce into the field is either on the proscribed list of plants pests—and therefore requires a permit—or it is exempt. The Stanford Model stratifies organisms into several risk categories, making it more quantitative and nuanced. Specifically, the Stanford Model stratifies organisms according to their risk in field trials. As shown in Figure 1, this universe can be divided in two ways:

- horizontally, according to risk categories, with higher risk as one goes toward the top of the pyramid; or
- by the oblique lines, dividing the universe of field trials according to technology; for instance, the far-left area is all field trials performed with organisms created by conventional breeding

or tissue culture, while the slice on the far right corresponds to field trials with recombinant DNA-modified organisms.

Conceptually, it should be clear that there is no particular enrichment of risk depending on technology. There are high-risk organisms—for example, the foot-and-mouth disease virus, African killer bees, rusts that infect grains, or highly invasive weeds such as kudzu—that require more caution in field tests whether or not they have been genetically modified in any way. Plants may be invasive, produce potent toxins, etc., but most are of negligible or low risk. Recombinant DNA technology affords no particular monopoly on safety, but it is far more precise and more predictable than the other techniques.

The Stanford Model resembles the approach that was taken in the National Institutes of Health/Centers for Disease Control (NIH/CDC) as described in the handbook *Biosafety in Microbiological and Biomedical Laboratories*. Now in its 5th edition, the handbook specifies the procedures and physical containment that are appropriate for research with microorganisms, including the most dangerous pathogens known. These microorganisms were stratified into risk categories by panels of scientists. Interestingly, unlike regulators' approach to recombinant DNA–modified organisms, even for the most dangerous pathogens the NIH/CDC approach only offers guidance to researchers but adherence is not compulsory.

Pilot project | The Stanford Model—applied only to plants in its first demonstration project—could easily accommodate different kinds of organisms, geographical regions, and preferences for more or less stringent regulation. In January 1997, the project assembled a group of approximately 20 agricultural scientists from five nations at a workshop held at the International Rice Research Institute (IRRI) in the Philippines. The purpose of the workshop was to develop a broad, science-based approach that would evaluate all biological introductions, not just those that involve genetically engineered organisms. The need for such a broad approach was self-evident—there was already abundant evidence that severe ecological risks can be associated with plant pests and "exotic," or non-coevolved, organisms.

As part of the pilot project, the IRRI conference participants evaluated and then stratified a variety of crops based on certain risk-related characteristics that are relevant to risk. A consensus among the participants was reached without serious difficulty, suggesting that it would be similarly possible to categorize other organisms as well.

The participants agreed at the outset that the following risk-based factors would be integral to a model algorithm for field-testing and commercial approval of all plant introductions:

- ability to colonize,
- ecological relationships,
- human effects,
- potential for genetic change, and
- ease or difficulty of risk management.

Each of the organisms evaluated during the conference was assessed for all five factors, and in the end the group placed all of the organisms into one of just two categories, those of lowest risk. Most of the common crop plants addressed were found to belong in Category 1 (negligible risk), with only a few ranked in Category 2 (low but non-negligible risk). One plant (cotton) was judged to be in Category 1 if it were field-tested outside its center of origin, and Category 2 if tested in the vicinity of its center of origin.

The group's analysis supported the view that the risks associated with field-testing a genetically altered organism are independent of the process by which it was modified and of the movement of genetic material between "unrelated" organisms.

This pilot represented only a first cut at devising a model. In actual practice, the new trait introduced into or enhanced in the parental plant (or other organism) would also need to be considered, so the "risk category" determined as described above would represent a sort of preliminary assessment subject to alteration. The introduction or enhancement of most traits (such as herbicide resistance in grains or the bifortification in Golden Rice) would add negligible or low risk and not change the risk category. The addition of genetic material about which there is minimal information would be considered of intermediate/uncertain risk and would bump up the preliminary risk category. The addition of certain higher-risk traits, such as heavy-metal accumulation or the synthesis of orally active drugs or potent toxins or allergens, might elevate the risk category by two levels.

It is important that, in the evolution of the Stanford Model, the factors taken into account were indifferent to either the nature of the genetic modification techniques employed, if any, or to the source(s) of the introduced genetic material. The participants agreed that whether conventional breeding techniques or recombinant DNA methods were used to modify an organism was irrelevant to the risk posed by an organism. They also agreed that combining DNAs from phylogenetically distant organisms—i.e., organisms from different genera, families, orders, classes, phyla, or kingdoms—was irrelevant to the risk posed.

In other words, the group's analysis supported the view that the risks associated with field-testing a genetically altered organism are independent of the process by which it was modified and of the movement of genetic material between "unrelated" organ-

isms. The Stanford Model suggests the utility and practicality of an approach in which the degree of regulatory scrutiny over field trials is commensurate with the risks, independent of whether the organisms introduced are "natural," non-coevolved (that is, "exotic"), or genetically improved by conventional methods or recombinant DNA techniques. Thus, the approach is consistent with the scientific consensus about the risks posed by genetically engineered organisms, as described at length above.

Flexibility | What, then, are the practical implications of an organism being assigned ultimately to a "risk category"? The level of oversight faced by an investigator who intends to perform a field trial with an organism in one or another of the categories could include: complete exemption, a simple "postcard notification" to a regulatory authority (without affirmative prior approval required), premarket review of only the first product in a given category, case-by-case review of all products in the category, or even prohibition (as is the case currently for experiments with the foot-and-mouth disease virus in the continental United States, for example).

A key feature of the Stanford Model is that it is sufficiently flexible to accommodate differences in regulatory authorities' preferences for greater or lesser regulatory stringency. Put another way, different national regulatory authorities could choose their preferred degree of risk aversion, some leaning more toward exemption and notification, others toward case-by-case review. However, as long as regulatory requirements were commensurate with the relative risk of each category and did not discriminate by treating organisms of equivalent risk differently, the regulatory methodology would remain within a scientifically defensible framework.

Under such a system, some currently unregulated introductions of traditionally bred cultivars and so-called "exotic" organisms considered to be of moderate or greater risk would probably become subject to regulatory review. But most recombinant DNA–modified organisms that now require case-by-case review would be regulated less stringently. A significant practical advantage would be that the vagaries of bureaucrats and bureaucracies would often be avoided: there would need to be far fewer case-by-case reviews by regulators and, therefore, far fewer opportunities for bureaucratic mischief or, in the United States, "major actions" that could become targets for NEPA litigation.

The introduction of such a risk-based system would rationalize significantly the regulation of field trials and would reduce the regulatory and other disincentives to the use of molecular techniques for genetic modification. It would achieve the fundamental purpose of regulation: circumscribing for review the products and field trials that need to be reviewed, and exempting those that do not.

In summary, the Stanford Model:

- stratifies all organisms according to risk and is indifferent to the technique (if any) of genetic alteration;
- is flexible;
- is scientifically defensible;
- permits various degrees of risk-aversion, permitting regulators discretion in a scientific context; and
- exempts field trials that should be exempt and captures field trials that should be reviewed.

An advantage of this approach is that it is analogous to existing, effective regulatory regimes, such as those for quarantine regulations for plant or animal pests, and also to the U.S. government's approach to researchers' handling of dangerous pathogens and other microorganisms in the laboratory. In other words, the approach is not fundamentally new and has worked well in practice for decades. Only politics and bureaucrats' self-interest have prevented its application to biotechnology.

Conclusion

Compared to its potential, the stunted growth of agricultural and animal biotechnology worldwide stands as one of the great societal and public policy tragedies of the past quarter-century. Unscientific, excessive, stultifying regulation, nationally and internationally, is a major reason for the failure of biotechnology to achieve its potential to bring greater food security to the poor and possibly to give rise to The Next Big Thing in American innovation.

This failure of public policy was entirely unnecessary. Biotechnology could have made far greater contributions to the production of food, fiber, and other products if only governments and international organizations had expended effort on devising scientifically defensible, risk-based regulation instead of on introducing, maintaining, and promoting unscientific, palpably flawed, debilitating regulatory regimes.

The British historian Paul Johnson wrote, "Left to themselves, the creative forces in society will always deliver, but keeping them reasonably free to do so is a perpetual grinding battle. It is one that must never be lost." When it comes to the nexus of science, technology, and public policy, many in our society are fighting that battle on the wrong side. R

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