GMO Regulatory Reform: The Way Forward

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Overview

I am a molecular biologist and geneticist and I was one of the first to apply molecular techniques in plant biology commencing in the 1970s. I have been involved in the regulatory issues around modern genetic modification – GM – since the early 1980s, when I served on the NIH Recombinant DNA Advisory Committee. I was also one of the authors of the 1987 National Academy of Sciences (NAS) White Paper titled: "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues."[1] Then, as now, there was no evidence that unique hazards attend the use of modern GM techniques or in the movement of genes between unrelated organisms, as clearly articulated in the NAS document. The paper further states:

- The risks associated with the introduction of R-DNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods.

and concludes that:

- Assessment of the risks of introducing R-DNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.

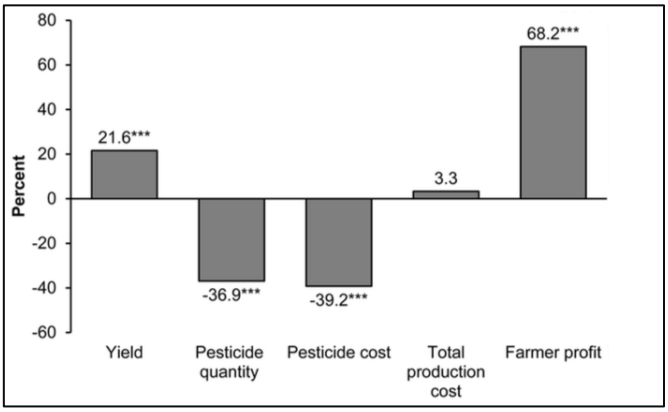
The President Obama's recent directive on GMO regulation creates an unprecedented opportunity for the EPA, USDA and FDA to 1) review the evidence that has accumulated in the intervening 30 years of biosafety research and field experience and 2) to move the regulatory system from *de facto* process-based to truly risk-based.

Going forward, it is critically important to facilitate the use of molecular genetic modification techniques in agriculture. The warming climate, among other factors, is changing pest and disease profiles and distributions. This demands far more rapid adaptation responses, particularly for crops, than can be achieved through the older breeding approaches. And because so many different crops and animals are being – and will be – affected, the participation of many more skilled scientists will be necessary to meet these challenges than just those employed by big biotech companies. Tragically, today our public sector agricultural scientists have all but ceased using GM techniques for crop and animal protection and improvement. This is largely because the cost and time involved in obtaining regulatory approval for a GMO release is simply prohibitive.

It is therefore imperative that the present regulatory restructuring yield a framework that is truly risk-based and readily traversed by the developer at reasonable cost. The kinds of decision trees that should be elaborated, albeit based on current knowledge and decades of experience, were already laid out as long ago as the 1989 NRC report titled: "Field Testing Genetically Modified Organisms: Framework for Decisions."[2] This is especially important in the face of emerging gene modification technologies, such as the CRISPR-Cas system, that provide unprecedented control over what genes are modified and how, something that has never been possible in the entire history of agriculture.

GMO Track Record: Safety, Economic, Environmental and Health Benefits

GM crops have been in commercial production for almost 20 years.[3] They have an impeccable safety record and multiple environmental benefits.[4,5] Despite anecdotal reports, often never published or subsequently retracted, no allergies, illnesses or deaths have been reproducibly linked to the consumption of GM food or feed anywhere in the world.[6,7,8]



GM crops have boosted yields and farmers' incomes[4,5]. The figure on the right provides a graphic illustration.[5] Environmental impacts for the period 1996-2012 include the application of 503,000 tons less pesticide (active ingredient), greenhouse gas reductions of 16 million tons CO_2 and increased soil carbon sequestration from no till farming estimated at more than 200 million tons CO_2.[9]

Consumers have benefitted not only through continuing low food prices, but also directly from decreased mycotoxin contamination of corn. GM Bt corn contains a bacterial gene that encodes a protein that is toxic to certain boring insect pests, but not to animals or people. Such insects bore holes in developing corn plants, allowing fungi to enter, grow and produce mycotoxins, compounds that are toxic and can be carcinogens for people and farm animals. Bt corn has been shown to contain 50-90% less mycotoxins than conventional corn.[10]

Scientific academies and scientific societies around the world concur that modern methods of genetic modification are as safe as those used by previous generations of plant and animal breeders, arguably safer.[7,11] Decades of research on GMO biosafety have simply failed to identify hazards unique to the use of GM technology for crop improvement. Quoting from a recent EU report on GMO research[12]:

"The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research, and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than e.g. conventional plant breeding technologies."

Until the development of modern GM techniques, breeders had to depend on either rare natural – or more recently – induced mutations (another name for genetic modifications) – to develop better crops. Today we know enough about genes to introduce a desired trait into an already highly productive plant or animal without the undesirable downsides of older methods.[13] It's worth pointing out that the history of plant and animal genetic modification extends back some 10,000 years. We created corn, not Mother Nature[14]; we created big, luscious heirloom tomatoes – Mother Nature's are tiny.[15]

Impediments to GMO Regulatory Reform.

Today, more than 60% of Americans believe that GMOs are unsafe. A recent poll of scientists and the public on GMOs gave startling results: only 37% of the public believes GMOs are safe, compared with almost 90% of scientists.[16]

Why? The reasons lie in the increasingly strident efforts of determined anti-GMO activists to convince the public that GMOs are bad, largely to further their own economic interests. Most prominent among these are certain NGOs and the organic food industry. Greenpeace and Friends of the Earth have conducted vigorous campaigns of misinformation about GMOs first in Europe, then around the world.[17,18] Indeed, Greenpeace remains adamantly against even the most benign and beneficial uses of GM technology in agriculture, such as the development and distribution of Golden Rice. Moreover, a recent, meticulously researched "Organic Marketing Report" documents how the organic food industry has systematically demonized GMOs, while advancing organically grown food as more healthful than conventionally grown food.[19]

It is important to recognize that opposition to technological advances is unique to neither GM technology nor food. Food irradiation has long been resisted in the U.S. and only recently has there been a gradual reintroduction of irradiation in such foods as ground meat and milk. As well, recent efforts to market "raw" milk have even sought to discredit time-honored public health measures such as milk pasteurization. Areas of traditional – and continuing – efforts to undermine well-supported public health measures include water fluoridation and vaccination. Nonetheless, the dedication of public health professionals has in this century, as in previous centuries, succeeded in overcoming uninformed and belief-based resistance to implement needed public health measures. A similar situation confronts agencies charged with the oversight of GMOs today.

Why GMO Regulatory Reform is Essential to the Future of Humanity

In some measure, the current regulatory tangle was created to reassure a dubious public that regulators were vigilant when GM techniques were first being used to modify organisms in agriculture. Yet both the original 1986 Coordinated Framework for Regulation of Biotechnology and its subsequent 1992 update implicitly acknowledged that the modification of organisms by GM techniques is not inherently hazardous, consistently stating that regulation should be based on the properties of the product, not the process.[20,21]

But that is not how the regulation has worked or works today, since only organisms modified by molecular techniques have been subjected to regulatory scrutiny under the Coordinated

Framework. Moreover, the regulatory process is fragmented among 3 agencies (the USDA, the EPA and the FDA), is excruciatingly bureaucratic and time-consuming (not infrequently taking years), and is undeniably expensive. Complying with the cost to develop and bring to market a single modification of an existing crop has been reported to cost as much at $135 million, about a third of which comprises the cost of compliance with current regulatory requirements.[22]

Tragically, the effort, time, and cost for regulatory approval have dried up the pipeline of biotechnology innovation and largely eliminated the participation of public sector researchers in using GM technology for crop improvement, while delivering no benefit to public health or environmental safety.[23] Ironically, it is this extremely "precautionary" approach exercised by the regulatory agencies that has virtually guaranteed that the only crops worth modifying would be the major commodity crops and the only organizations that could afford to modify them would be the big biotech companies.

There are profound humanitarian implications should the current regulatory environment not improve dramatically. Global agricultural productivity increases are even now lagging behind population growth[24] – and that's without figuring in the growing impact of climate warming.[25] The future lies in "agricultural intensification".[21] We will need to produce more food using less water on the land already farmed if we're to preserve what remains of our rich biological heritage. As well, the warming climate poses severe challenges for crops domesticated in a milder climate because the higher temperatures both directly depress crop yields and indirectly reduce productivity through changing disease and pest profiles. Genetic modification of plants, in which the U.S. currently leads, will be one of the most critical contributors in producing the 50-70% more food the FAO says will be required to feed the 9 or 10 billion people expected in coming decades, but only if the regulatory burdens are eased.[26,27] We will have to adapt much more rapidly to the many threats posed by climate warming than can be done by traditional methods, even as we seek to coax more crop from each drop of water and square meter of land.

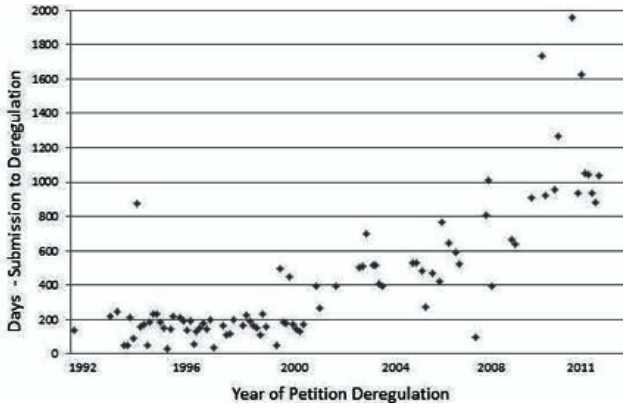
This means improving many different traits and protecting many different crops from many different pathogens and pests in many different countries. The mission of agricultural scientists, in our land grant universities and our USDA research stations, as well as national agricultural research organizations around the world, is to help farmers with the problems they identify on their farms with their crops and animals. In the U.S., these scientists, with just a few exceptions, have not and do not use molecular techniques to solve agricultural problems, simply because they cannot afford to comply with the regulatory requirements for getting their improved varieties "deregulated." **A primary goal of regulatory reform, then, should be to facilitate such work by vastly lowering the regulatory barriers for low-risk applications.**

Lowering Regulatory Barriers

Neither the Coordinated Regulatory Framework of 1986 nor its subsequent elaborations are the problem. Indeed, the verbiage in the 1992 update is clear and precise, describing: "….a risk-based, scientifically sound approach to the oversight of planned introduction of biotechnology products into the environment that focuses on the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created. Exercise 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 of technique."

The problem is that GM organisms continue to be regulated *as if* they were inherently risky. Said another way, the regulatory framework asserts that regulatory oversight should be based on risk, but as it has been implemented, it is *de facto* process based. Thus crops modified by older, less precise methods, such as chemical mutagenesis and radiation, are subject to no regulatory oversight, while crops produced using recombinant DNA technology must comply with extensive regulatory scrutiny, regardless of existing evidence and experience with similar modifications. Indeed, even as experience with GM crops has accumulated, the timelines for approvals have grown ever longer, as illustrated by the graph on the right showing data from the USDA[28].



As currently practiced, the regulatory system is functionally locked into the grossly overestimated potential for hazardous impacts perceived when the regulatory framework was first implemented. **What is missing is a rigorous and transparent process for integrating experience gained over the past 30 years of field-testing, commercialization and biosafety research**. As a colleague states the problem:

"The biggest bureaucratic failure has been the lack of any meaningful update to the Coordinated Framework to recalibrate the nature and extent of regulatory oversight so as to restore a closer relationship between the degree of regulatory scrutiny and the potential for hazard that contributes to risks that might need management. There is low hanging fruit to be plucked here that, when harvested, would drastically reduce the exposure of regulatory agencies to the harassment by procedural lawsuits from professional opponents of agricultural innovation."[29,30]

In the early days of R-DNA research, it was the NIH's Recombinant DNA Advisory Committee (RAC) that developed guidelines for the conduct of R-DNA research. The initial version of the NIH Guidelines for Recombinant DNA Research were markedly precautionary because little was known about the phenotypic effects of transferring genes between unrelated species.[31] However, the technology proved so powerful that it was very rapidly adopted, even with the initially onerous laboratory containment requirements, and experience with the technology and with transgenic organisms accumulated rapidly – without incident. The properties of recombinant organisms proved to be predictable from knowledge of the parent organism and the added gene or genes. The RAC considered the accumulating evidence through the early years and both relaxed containment requirements and progressively exempted low-risk categories from regulatory review entirely. The successive modifications to the guidelines were published in the Federal Register for comment and adopted after consideration of the input received.

Moreover, the original guidelines contained prohibitions on certain types of experiments, such as the cloning of toxin genes into *E. coli*, the workhorse of R-DNA research. The way the RAC approached such a specific prohibition was to assemble a panel of experts with experience in

working with the native organisms that produce such toxins to review and discuss the potential for creation of an organism more hazardous than the native one by such cloning experiments. In this particular case, it became evident that working with a toxin gene expressed in *E. coli* was actually significantly less hazardous than working with the native organism, simply because the laboratory strains lack the additional genetic apparatus necessary to deliver the toxin to the requisite target cells.[32] The prohibition was, in time, relaxed based on this expert input. The essential point here is that the RAC developed a mechanism to continuously reexamine and modify the guidelines based on expert knowledge and accumulating experience. Moreover, the process was transparent, as the RAC meetings were open to the public and proposed modifications to the guidelines were published for public comment in the Federal Register. Much of what was severely restricted or prohibited in the early guidelines is now exempt from regulation simply because early fears of potential hazards proved groundless.[33]

This process of continuous reexamination and reconsideration of what does and does not need regulatory oversight all but stopped when jurisdiction over the introduction of R-DNA organisms into the environment was assumed by the EPA, USDA and FDA under the 1986 Coordinated Framework for the Regulation of Biotechnology.[21] The objectives of regulation – real risks and hazard – were subverted from the outset, as the regulatory agencies sought to extend and interpret definitions to capture RDNA-modified organisms within the regulatory scope of existing laws written to regulate toxic chemicals, plant pathogens, drugs and food additives.

The only path out of the trap of process-based regulation is to establish a science- and experience-based process for creating categorical exemptions for low-risk applications. This would simultaneously reduce the regulatory workload for the agencies, dramatically lower development costs for both public and private sector enterprises, and spur innovation. As well, this would reduce the requirement for low-risk introductions to comply with the requirements of the National Environmental Policy Act (NEPA) invoked by "major federal actions."[34] It should be noted that the necessity to obtain USDA APHIS approval, which triggers NEPA compliance, is not required for crops modified by conventional plant modification technologies, even those, such as radiation and chemical mutagenesis, that are genetically far more disruptive than modern molecular techniques.[35]

The advent of a new generation of techniques for modifying genes and levels of gene expression, including RNAi and targeted nuclease technologies, such as the CRISPR-Cas system, heightens the importance of developing and implementing a truly risk-based regulatory system.[36] These techniques have far lower potential for creating unintended hazards than older techniques because they increase the ability to focus on one (or a small number) of genes to modify their structure and/or expression in predictable ways. Subjecting crops modified by such precise techniques to regulatory scrutiny vastly greater than that exercised over crops subjected to random chemical and radiation mutagenesis makes no sense.

A Risk-based Exemption Framework

A straight-forward process for exempting negligible-risk categories of GMOs for environmental release is easily defined, however difficult to implement. The NIH RAC process described above defines the steps: 1) convene expert groups, 2) review the evidence, 3) define exempted

categories, 4) publish in the Federal Register, 5) evaluate feedback, 6) implement. The 1989 NRC report titled "Field Testing Genetically Modified Organisms: Framework for Decisions" provides an excellent collection of decision trees that can be adapted and refined for the present purpose.

The key to the success of such an exemption process lies is the composition of the expert groups. It is critical that an unbiased group of individuals with deep expertise in agriculture/aquaculture and in genetic modification be brought together for the present purpose. Moreover, I believe that this should be the nexus of inter-agency coordination. That is, the process should lead to the creation of decision trees applicable within all three agencies that a developer can quickly traverse to determine whether his/her organism or product is exempt or requires regulatory scrutiny and to identify the relevant agency if it does. The process should be convened as a standing committee under the auspices of the National Academies of Science, but involve all three regulatory agencies. This "expert" process is very vulnerable to being gamed even in the (laudable) interest of broad representation, so it is essential that membership be based on the expertise, scientific stature and relevant practical experience of each member, not on the individual's beliefs about or stance on GMO issues.

I recognize that the process I am suggesting will bring extraordinary pressure from anti-GMO activists. But if the objectives of the president's directive are to be achieved, it is essential not to prolong and enlarge the negative mythology surrounding GMOs. This means acknowledging through exemption that whole categories of applications, such as precisely targeted gene inactivation or the transfer of disease resistance genes from both closely and not-so-closely related organisms, to long-used crop plants, pose negligible risks to human health and the environment. Only when such low-risk applications are freed from regulatory burdens will it be possible to unleash the capacity for innovation in the large fraction of the relevant scientific community that resides in our universities and government research organizations, as well as in small companies. I further believe that the categorical exemption process can be developed and implemented gradually and sensibly enough to minimize the probability of blowback and legal assaults.

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