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Review

The regulation of agricultural biotechnology: science shows a better way

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National and international regulation of recombinant DNA-modified, or 'genetically engineered' (also referred to as 'genetically modified' or GM), organisms is unscientific and illogical, a lamentable illustration of the maxim that bad science makes bad law. Instead of regulatory scrutiny that is proportional to risk, the degree of oversight is actually *inversely* proportional to risk. The current approach to regulation, which captures for case-by-case review organisms to be field tested or commercialized according to the techniques used to construct them rather than their properties, flies in the face of scientific consensus. This approach has been costly in terms of economic losses and human suffering. The poorest of the poor have suffered the most because of hugely inflated development costs of genetically engineered plants and food. A model for regulation of field trials known as the 'Stanford Model' is designed to assess risks of new agricultural introductions – whether or not the organisms are genetically engineered, and independent of the genetic modification techniques employed. It offers a scientific, rational, risk-based basis for field trial regulations. Using this sort of model for regulatory review would not only better protect human health and the environment, but would also permit more expeditious development and more widespread use of new plants and seeds.

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'Genetic engineering' is not new

Over many millennia, there has been a virtually seamless continuum of genetic improvement of crops with increasingly sophisticated techniques [1]. Recombinant DNA modification, a term I will use interchangeably with 'genetic engineering', was introduced as part of this progression of technologies during the 1970s. Thus, because genetic modification, or improvement, has been with us for centuries, 'genetically modified organism' and its abbreviation 'GMO' – commonly used nomenclature – are unfortunate choices of terminology. Defined arbitrarily as organisms containing genes transferred across species lines – but only when accomplished by recombinant DNA techniques – it ignores that genetic modification is achieved using many technologies and that recombinant organisms are not a meaningful 'category'.

Millions of 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. Wide crosses have been performed for almost a century and thousands of such 'non-molecular transgenic varieties' (as they might be called) are in commerce around the world. Examples include:

- *Triticum agropyrotriticum*, a man-made 'species' that resulted from combining genes from bread wheat and a grass called quackgrass or couchgrass, that contains all the chromosomes of wheat and one extra whole genome from the quackgrass.
- Triticale, also a man-made grain, a wheat–rye hybrid.
- Pluots and apriums, plum–apricot hybrids.

T. agropyrotriticum is a particularly apt example. Throughout development, from field-testing through scaling up and commercialization to being fed to animals and humans, neither regulators nor activists were concerned with whether the tens of thousands of genes from quackgrass would make *T. agropyrotriticum* more weedy or whether any of the expression products were toxigenic or allergenic. Nor has the pluot, commonly found at summer farmers' markets, elicited any resistance from activists or scrutiny from regulators.

By contrast, if someone were to move a single gene from quackgrass into Triticum or from plum to apricot using recombinant DNA techniques, the new constructions would be subject to expansive, extensive, lengthy, and debilitating regulatory regimes.

Most agricultural crops are the products of hundreds, if not thousands, of years of genetic improvement. Maize, for example, has undergone drastic, gradual modification, from the original grass-like plant with primitive, meager kernels, into modern maize, with regularly arranged kernels replete with carbohydrate, oil, and protein [2].

A more recent example of the irrationality of current conceptions of 'natural' versus 'genetically engineered' is Golden Rice, several varieties biofortified with beta-carotene, the precursor of vitamin A. Ref [3] shows the entire 'pedigree' of the immediate precursor of Golden Rice, IR64 – a strain of rice widely used in many parts of the world – as well as the addition of two genes that convert IR64 into Golden Rice. What is astonishing about this construction is that for regulatory purposes, all of the complex genetic changes, including mutations, recombinations, deletions, and translocations leading to IR64 are somehow considered 'natural' – and therefore elicit no concern or review – while the insertion into exactly known sites of two well-characterized 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. Although 'GMOs' (or variations on the theme) are not a genuine, meaningful category, in most regulatory regimes around the world, merely the use of recombinant DNA techniques is the trigger for draconian, dilatory, and expensive regulatory regimes.

Benefits and obstacles

Genetically engineered plants have persuasively demonstrated extraordinary benefits:

- Increased yield, which permits conservation of cultivated land and avoidance of upslope farming.
- Decreased use of chemical pesticides, which leads to less runoff and fewer poisonings. For example in China, the use of Bt cotton has substantially reduced poisoning incidents by pesticides among farmers and their families [4].
- Reduced water requirements with drought resistant or saline tolerant varieties may be among the most important applications worldwide. With recurrent droughts over southern Europe, Australia, parts of the United States, and much of sub-Saharan Africa, small improvements in water requirements for agriculture can make a large difference in the yields and cost-effectiveness of farming.
- Shifts in herbicide usage lead to the use of more environmentally friendly herbicides and increased no-till farming, resulting in lower soil erosion, less runoff, and less carbon dioxide released to the atmosphere.
- Decreased content of fungal toxins in food and feed, and correspondingly reduced incidence of illness in animals and humans.

In spite of these benefits and the absence of any unanticipated or unique negative effects, the technology has encountered various policy and public relations obstacles. A number of 'pseudo-crises' – high-profile incidents that falsely implied significant risks of genetic engineering, fomented by fear-mongering non-governmental organizations, one-sided journalism, and the expansionist tendencies of bureaucrats – have led to flawed public policy and over-regulation of genetic engineering techniques and their products.

The scientific basis of regulation

There exists a decades-old scientific consensus about the need for a more rational, risk-based approach to the regulation of both field trials and commercialization of genetically engineered plants. In 1987, the U.S. National Academy of Sciences (NAS) published a white paper on the planned introduction of genetically engineered organisms into the environment [5]. It noted that recombinant DNA techniques provide a powerful and safe means for modifying organisms, and it predicted that the technology would contribute substantially to improved health care, agricultural efficiency, and the amelioration of many pressing environmental problems. The paper had wide-ranging impacts in the United States and internationally. 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 this white paper, the National Research Council (NRC), the research arm of the NAS, concluded that 'no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes,' whether in the laboratory, in the field, or in large-scale environmental introductions [6]. The NRC report supported this statement with extensive discussions of experience with plant breeding and the cultivation of these pre-recombinant DNA genetically modified plants and microorganisms:

- 'Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits. As the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants.'
- '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.'
- '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.'
- As a consequence, '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.'

Thus, the NRC articulated some of the principles that should underlie the regulatory oversight field trials of plants, and subsequently these principles have been reiterated repeatedly by countless scientific bodies. The essence is that the mere fact that an organism has been modified by genetic engineering techniques should not determine how the organism is regulated. This was emphasized yet again in the comprehensive report from the U.S. National Biotechnology Policy Board (on which I served as a charter member), which was established by the U.S. Congress with representation from the public and private sectors. The report 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' [7]. The report went even further, concluding, '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.' This is true in general for this technology and its products, particularly for parts of the world where subsistence farming predominates.

Various other national and international groups, including the American Medical Association, the United Kingdom's Royal Society, and the UN's Food and Agriculture Organization and World Health Organization, have repeatedly echoed or extended these conclusions. For example, a joint statement from the International Council of Scientific Unions' (ICSU) Scientific Committee on Problems of the Environment (SCOPE) and the Committee on Genetic Experimentation (COGENE) concluded 'The properties of the introduced organisms and its target environment are the key features in the assessment of risk. Such factors as the demographic characterization of the introduced organisms; genetic stability, including the potential for horizontal transfer or outcrossing with weedy species; and the fit of the species to the physical and biological environment ... apply equally to both modified or unmodified organisms; and, in the case of modified organisms, they apply independently of the techniques used to achieve modification' [8]. That is, it is the characteristics of organism itself, and not how it was constructed, that is important.

Similarly, the report of a NATO Advanced Research Workshop concluded, 'In principle, the outcomes associated with the introduction into the environment of organisms modified by recombinant DNA techniques are likely to be the same in kind as those associated with introduction of organisms modified by other methods. Therefore, identification and assessment of the risk of possible adverse outcomes should be based on the nature of the organism and of the environment into which it is introduced, and not on the method (if any) of genetic modification' [9].

Other analyses have focused specifically on the food safety aspects of gene-spliced organisms and their derivatives. For example, in a 1993 report the Paris-based Organization for Economic Cooperation and Development (OECD) described several concepts related to food safety that are wholly consistent with, and expand upon, the consensus discussed above [10]:

- '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.'
- '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.'

Finally, a comprehensive analysis of food safety published in 2000 by the Institute of Food Technologists addressed both the scientific and regulatory implications of foods derived from genetically engineered organisms and specifically took current regulatory policies to task. The report concluded that the evaluation of genetically engineered organisms and the food derived from them 'does not require a fundamental change in established principles

of food safety; nor does it require a different standard of safety, even though, in fact, more information and a higher standard of safety are being required' [11]. The report went on to state unequivocally that theoretical considerations and empirical data do 'not support more stringent safety standards than those that apply to conventional foods.'

What could be clearer than this consensus about the appropriate basis for the oversight of genetically engineered plants in the field and in the food supply?

Principles of regulation

In addition to the consensus described above specifically for the products of genetic engineering, there are certain general principles of regulation 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.
- If the scope of regulation – i.e. the regulatory net or the trigger that captures field trials or the finished product for review – is unscientific, then the entire approach is unscientific.

Consequences of flawed regulation

All of the principles of regulation described above have been largely ignored. Current regulatory regimes are unscientific, process-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.

Increased research and development costs

The compliance costs of regulation for the development of an insect-resistant and a herbicide-resistant maize have been calculated to be between USD 6 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.

Fewer products in the pipeline with reduced benefits for farmers and consumers

The costs and uncertainty created by the regulatory milieu have inhibited agricultural innovation and product development, decreased commercialization of already-developed genetically engineered crops and decreased the potential for new, improved varieties of fruits and vegetables, tree fruits and nuts, and nursery and landscape crops. That is to say, development is economically viable primarily for commodity crops, which are grown at vast scale.

In 2009, the total area of biotech crops was around *134 million hectares, making it the most rapidly adopted crop technology in history, an 80-fold increase from 1996 to 2009*. Nobody has yet been able to calculate the economic losses from excessive, gratuitous regulation, but it unquestionably imposes a huge punitive tax on a superior technology; with more rational, science-based regulation there would be a far greater shift to genetically engineered crops, with additional traits and species developed and commercialized. Putting it another way, the opportunity costs of flawed, unscientific public policy have been enormous, and as usual, most of those costs have been imposed on the poor.

Pseudo-crises and litigation

Pseudo-crises have led to public relations debacles, flawed public policy, endless debate over inconsequential issues like, coexistence, of genetically engineered and conventional crops, acceptable tolerances for 'contamination', and labeling, as well as costly court trials. One well-known example is the StarLink case where the US Environment Protection Agency gave split approval of maize, sanctioning it for animal but not human consumption. After it was subsequently detected in human foodstuffs [12], the regulatory and civil penalties to the company that developed the StarLink for this inconsequential 'transgression' were substantial (even though not a single person suffered any adverse effects). Other pseudo-crises include the (false) alarms over killing of Monarch butterflies and the contamination of land races from horizontal gene transfer in Mexico. All of these are based on inaccurate or fraudulent reports, or results taken out of proper context.

Vandalism and intimidation of academics

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 publically known. Researchers have been injured, research destroyed, and in Germany two universities responded to the threats of activists by banning the testing of recombinant DNA-modified plants, an appalling example of cowardice and abdication of academic freedom.

Malnourishment, illness, and deaths

Malnutrition claims thousands of lives per day, many of which could be saved if governments and international organizations would change their hostile attitudes and policies toward genetic engineering. The resulting greater availability of improved crop varieties would enhance food security for poor farmers.

The 'Stanford Model' for risk-based regulation

It is easy to complain about unscientific, non-risk-based regulatory regimes. But there are better proven alternatives, and science shows the way. One is the 'Stanford Model' for risk-based regulation, which was developed in the 1990s [13]. The Stanford Model stratifies organisms according to their risk in field trials. This universe can be divided in two ways (Fig. 1):

- Horizontally, according to risk categories, with higher risk as one goes toward the top of the pyramid.
- By the oblique lines, dividing the universe of field trials according to technology: the green area is all field trials performed with organisms created by conventional breeding or tissue culture, for example, while the area to 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 can be high-risk organisms – for example foot and mouth disease virus, African killer bees, rusts that infect grains, or highly invasive weeds

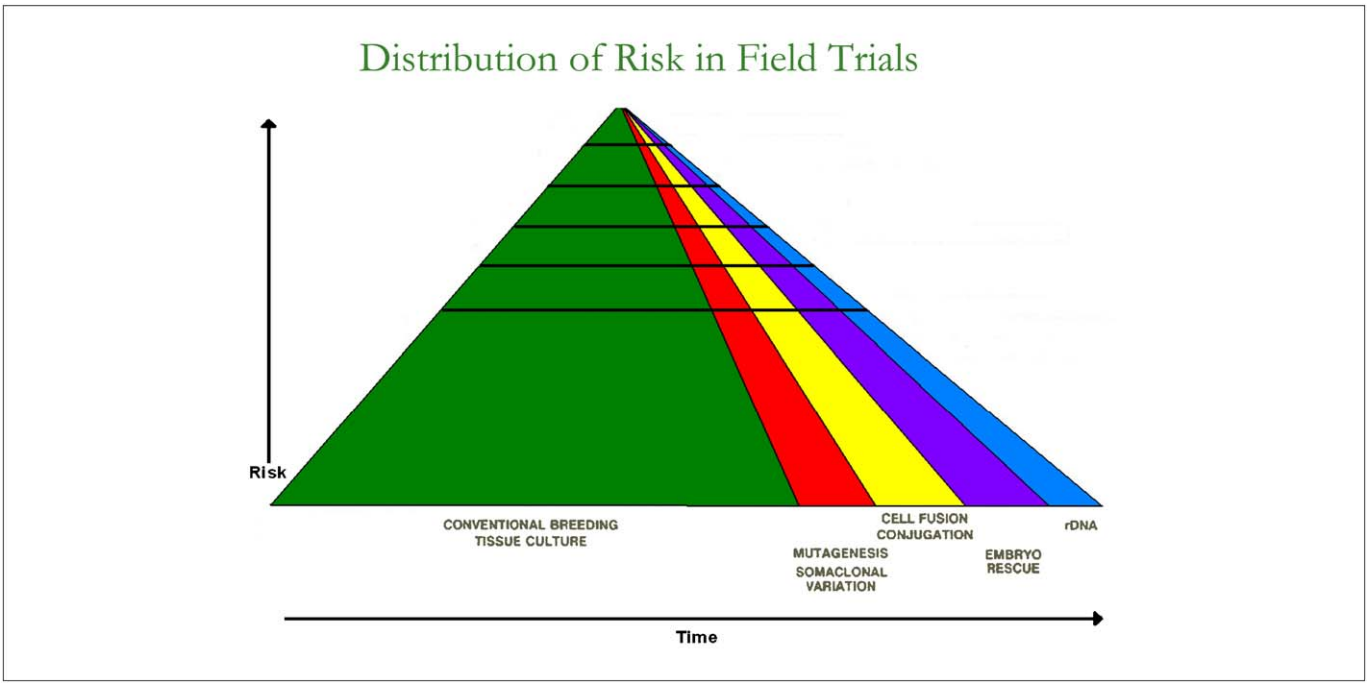

FIGURE 1
Distribution of risk in field trials.

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 in general they are of negligible or low risk. Recombinant DNA technology affords no particular monopoly on safety, but on average, it is far more precise and more predictable than the other techniques.

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 more quantitative and nuanced 'Stanford Model', which stratifies organisms into several risk categories, more closely resembles the approach that was taken in the National Institutes of Health/Centers for Disease Control (NIH/CDC) handbook *Biosafety in Microbiological and Biomedical Laboratories*, now in its 5th edition, which specifies the procedures and physical containment that are appropriate for research with microorganisms, including the most dangerous pathogens known [14]. These microorganisms were stratified into risk categories by panels of scientists. Interestingly, unlike regulators' approach to recombinant DNA-modified organisms, the NIH/CDC approach – even for the most dangerous pathogens – is only to offer guidance to researchers but not to make adherence compulsory.

The Stanford Model – applied to plants in its first demonstration project – can be readily applied to 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 5 nations at a workshop held at the International Rice Research Institute (IRRI), in Los Baños, 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 'exotics', 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, or traits, to be considered in order to estimate overall risk. Consensus 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 introductions:

- Ability to colonize.
- Ecological relationships.
- Human effects.
- Potential for genetic change.
- Ease or difficulty of risk management.

Each of the organisms evaluated during the conference was assessed for all 5 factors, which enabled the group to come to a global judgement about the organism's risk category. Most of the common crop plants addressed were found to belong in Category 1 (negligible risk), while a few were 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.

It cannot be over-emphasized that in the evolution of this 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 the use of conventional breeding techniques or recombinant DNA methods to modify an organism was irrelevant to risk. 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 of an organism.

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' organisms. 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 or have been genetically improved by conventional methods or gene-splicing techniques. Variations and refinements of this approach are possible, of course; Professor Wayne Parrott has suggested that the risk category could be adjusted depending on the trait introduced – a gene that enhances weediness or that expresses a potent toxin or allergen, for example, might bump the organism into a higher risk category (Parrott, personal communication).

What, then, are the practical implications of an organism being assigned 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 foot-and-mouth disease virus in the United States).

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. Putting it 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 are commensurate with the relative risk of each category and do not discriminate by treating organisms of equivalent risk differently, the regulatory methodology will remain within a scientifically defensible framework.

Under such a system, some currently unregulated introductions of traditionally bred cultivars and so-called 'exotic', or non-coevolved, organisms considered to be of moderate or greater risk would probably become subject to regulatory review, whereas many recombinant DNA-modified organisms that now require case-by-case review would probably be regulated less stringently. The introduction of such a risk-based system would rationalize significantly the regulation of field trials and it would reduce the regulatory and other disincentives to the use of molecular techniques for genetic modification.

By making possible accurate, scientific determinations of the risks posed by the introduction of an organism into the field, this regulatory model fosters enhanced agricultural productivity and innovation, while it protects valuable ecosystems. It offers regulatory bodies a highly adaptable, scientific paradigm for the oversight of plants, microorganisms, and other organisms, whether they are 'naturally occurring' or non-coevolved organisms, or have been genetically improved by either old or new techniques. The outlook for the new biotechnology applied to agriculture, especially environmentally friendly innovations of particular benefit to the developing world, would be far rosier if governments and international organizations expended effort on perfecting such a model instead of on introducing and maintaining unscientific, palpably flawed, debilitating regulatory regimes.

Advantages of the Stanford Model

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

One great advantage is that it is analogous to existing regulatory regimes, such as those for quarantine regulations for plant or animal pests, and also to the U.S. government's approach to handling dangerous pathogens or other microorganisms in the laboratory. In other words, the approach is not fundamentally new and has worked well in practice for decades.

Summary

Compared to its potential, the stunted growth of agricultural biotechnology worldwide stands as one of the great societal tragedies of the past quarter century. Unscientific, excessive, stultifying regulation, nationally and internationally, is a major reason for the failure of agricultural biotechnology to achieve its potential to benefit the poor. Scientists, regulators, and politicians must find more rational and efficient ways to guarantee public health and environmental safety while encouraging new discoveries. Science shows the path, and society's leaders – secular and religious – must take us there.

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