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A Risk-based Approach to the Regulation of Genetically Engineered Organisms

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Current regulatory regimes for genetically engineered crops fail to use a scientifically defensible approach or tailor the degree of regulatory review to the level of actual hazard or risk. We describe a rational way forward.

The use of molecular techniques for genetic engineering (GE), also known colloquially as 'genetic modification' (GM), offers plant breeders the tools to make old crop plants do spectacular new things. For a quarter-century, GE crops have been the most scrutinized foods in human history, despite a lack of scientific justification for such a burden. Although study after study—formal risk assessments as well as observations of 'real-world use'—have failed to show any new or incremental risks associated with GE, there has been no rationalization or reduction of the regulatory burden placed on GE crops. If anything, regulatory stringency continues to increase. As a deeper understanding of biology expands the range of technologies available for precision breeding, including genome editing, synthetic biology, oligo-directed mutagenesis, agro-infiltration, grafting onto transgenic rootstock and reverse breeding, removing unnecessary regulatory obstacles should be a high priority.

In this article, we describe a risk-based approach, building on that outlined originally by the National Research Council (NRC; Washington, DC) report in 1989 (ref. 1) and then later in the 'Stanford Model' for risk assessment[2]. With the US regulatory framework currently being re-evaluated, and with half a century of experience with transgenic organisms and almost two decades of experience with commercial GE crops in hand, the time is right to adopt such a risk-based regulatory approach.

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20 years of marketed GE crops

In some 30 countries worldwide, >18 million farmers are using GE crop varieties on more than 175 million hectares to produce more consistent and often higher yields with lower inputs and reduced environmental impact[3]. However, most of the acreage of these new varieties is dedicated to growing a small number of commodity crops cultivated at vast scale and designed to resist pests or tolerate herbicides.

The plants already commercialized have delivered substantial benefits to growers, consumers and the environment. Nevertheless, many of the greatest long-term contributions of GE and related technologies applied to agriculture are unlikely to be realized for many years. New crop varieties have been developed that tolerate drought and other water-related stresses, utilize soil and applied nutrients for more efficient plant growth, provide needed micronutrients to deficient diets ('bio-fortified' crops) and synthesize high-value-added molecules such as pharmaceuticals ('biopharming'), but only a few of these are currently available commercially[4]. Prohibitively high regulatory costs associated with commercial-scale field trials and other approval requirements mean that many of these promising varieties never make it to market[5].

Ideally, the extent of regulatory scrutiny should be commensurate with the level of risk[6,7], but all the regulatory regimes for the field trials and commercialization of GE crops around the world fail this test; the degree of regulatory scrutiny in most cases is actually *inversely* proportional to the risk. Such regulatory approaches are neither scientifically defensible nor justifiable, given both the global experience with GE crops and the current level of understanding of plant genomes.

Why regulation is ripe for reform

The approach proposed here for the regulation of plant biotech refines a model first described in this journal almost two decades ago[2]. For several reasons, it is appropriate for such an approach finally to be implemented:

- From the beginning of the use of molecular techniques for genetic engineering in the 1970s, authoritative reports by scientists have concluded that GE presents no unique or different risks in comparison to other forms of breeding and genetic alteration[1,8,9].
- Those conclusions have been reiterated many times by other authoritative reports, most recently from the United Kingdom[10–12] and Canada[13].
- Nothing has come to light in the past 40 years that contradicts the initial conclusion. GE crops have been in commercial production since 1996 without unexpected effects on ecosystems or a single documented adverse effect on human or animal health[14–16]. As scientists predicted early on, they have posed no unique or incremental risks different from those posed by crop varieties produced through conventional breeding techniques.
- Since the advent of the prototypic GE technique of the 1990s—recombinant DNA technology—molecular biology has provided a variety of advances in genetic modification techniques. These include various tools for genome editing (such as zinc-finger nucleases (ZFNs), transcription-

activator-like effector nucleases (TALENs) and in particular clustered regularly interspersed short palindromic repeats (CRISPR)-Cas9) that are even more precise and predictable.

On 2 July 2015, the administration of US president Barack Obama announced an initiative "directing the three federal agencies that have oversight responsibilities for [biotechnology] products—the Environmental Protection Agency (EPA; Washington, DC), the Food and Drug Administration (FDA; Silver Spring, MD), and the Department of Agriculture (USDA; Washington, DC)—to update the Coordinated Framework [for the Regulation of Biotechnology], develop a long-term strategy to ensure that the system is prepared for the future products of biotechnology, and commission an expert analysis of the future landscape of biotechnology products to support this effort"[17].

The memorandum commits to "ensuring that product evaluations are risk-based and grounded in the best science available, including regularly adjusting regulatory activities based on experience with specific products and the environments into which those products have been introduced."

The current approach of federal regulatory agencies does not meet that commitment, but the proposal outlined here would do so.

A brief history of genetic modification

As first detailed by Darwin in his *On the Origin of Species*, intentional breeding and selection have led to profound changes in morphology and behavior for many crop plants. For example, cabbage and cauliflower are the same species, and both are very different from their wild progenitor. Darwin's observations have now been refined by the realization that (with the exception of some traits affected by epigenetics) changes in the appearance and behavior of a plant are mediated by alterations in its DNA. Studying such changes and comparing them to those created by GE and the newer genome-editing technologies provide a robust baseline from which to evaluate the safety of changes in the genome.

Over many millennia, there has been a virtually seamless continuum of genetic improvement of crops using increasingly sophisticated techniques. Most agricultural crops are the products of hundreds, if not thousands, of years of genetic improvement by breeding. Corn, or maize, for example, has undergone gradual but drastic modification that converted it from the original grass-like plant, teosinte, which has only primitive, meager kernels, into modern varieties whose kernels bulge with carbohydrates, oil and protein. Modern bread wheat is a hexaploid species created from two separate hybridizations. The second was the cross of a wild grass, itself an interspecific hybrid, to emmer wheat[18], probably in the field of an ancient farmer in the Fertile Crescent. Thus, bread wheat never existed in nature untouched by human intervention[19].

When plant breeders have exhausted the genetic resources (germ, plasm) within their crop's species, they have employed several techniques, such as mutagenesis and wide-cross hybridization, to introduce new genes or alleles into their cultivars. By the middle of the past century, X-rays and other mutagens were being used routinely and at scale to obtain a range of genetic changes, from point mutations to translocations in interspecific hybrids; the latter allowed pieces of chromosomes from wild species to integrate or translocate onto crop chromosomes[20]. Mutation breeding is now routinely accomplished with other sources of ionizing radiation and with mutagenic chemicals[21]. The United Nations' Food and Agricultural Organization (FAO; Rome)/International Atomic Energy Agency (IAEA; Vienna) maintains a database that currently lists >3,000 known plant varieties developed through mutagenesis[22].

In wide-cross (interspecific and intergeneric) hybridization, the parental plants may be sufficiently compatible to produce a viable zygote, but often are not compatible enough to permit normal embryo or endosperm development[23]. In many such cases, the embryos can be 'rescued' in culture using techniques developed as long ago as the 1930s. Even with rescue, incompatibility of parental chromosomes can cause sterility, which may be overcome by doubling the number of chromosomes with colchicine, a mitotic inhibitor.

Many crops contain genes crossed in from wild relatives that have no history of safe use and that may even be known to produce toxins or allergens. In wide-cross hybridization, the genes or alleles of interest are moved into the crop—along with countless other genetic changes of unknown function, including those that potentially could alter the weediness of the plants or the allergenicity, toxicity or nutritional value of foods derived from them[24]. Nevertheless, such 'non-recombinant DNA transgenic varieties' (as they might be called) have been introduced safely into commercial cultivation around the world for more than a half-century without the need for premarket regulatory approvals. Examples include strains of wheat, rice, tomato, potato, sugar beet, pumpkin, oat and several others[25]. It is notable that none of these efforts has ever resulted in unexpected hazards, other than some predictable increases in the levels of known toxicants[26]. Thus, the track record shows that plant breeding, even using relatively crude techniques, is one of the safest technologies in history.

It is not surprising, therefore, that no country other than Canada has determined that there is a need to enact laws or establish regulations governing the testing or commercial introduction of wide-cross hybrids or mutant varieties. In contrast, when recombinant DNA is used to transfer just one known, well-characterized gene—as opposed to countless unknown genes in the examples described above—the result is commonly but erroneously perceived to raise unique safety concerns and is subject to intensive, expensive, dilatory case-by-case regulatory review.

The scientific basis for regulation

The US NRC concluded in 1987 that the *product* of genetic modification and selection should be the primary focus for making decisions about the risks of environmental introduction of a plant or microorganism, not the *process* by which the products were obtained[27]. Their report concluded that evaluation of experimental field testing should be based on three considerations:

- Familiarity: that is, 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.

The essence of these principles is that the mere fact that an organism has been modified by recombinant DNA or other molecular techniques has no bearing on the degree of hazard or level of risk and therefore should not determine whether (or how stringently) the organism is regulated.

Echoing and extending these and other scientific analyses, a 1992 report to the US National Institutes of Health (NIH, Bethesda, MD) from the US 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*"[28] (emphasis added).

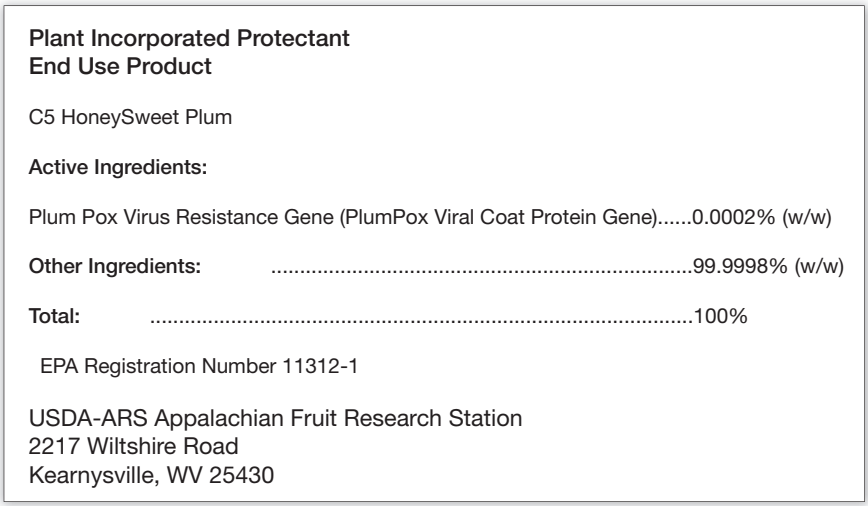

Figure 1 Label originally proposed by the EPA for virus-resistant plum. The active ingredient is the percentage of the plum DNA that is transgenic. Source: EPA (ref. 81).

This last observation is important, because the National Biotechnology Policy Board report is one of very few scientific assessments to have performed comparative risk assessment and to have recognized explicitly the social costs associated with inhibiting the development of a beneficial technology. For three decades, those costs have been high.

In addition to conforming to the points of scientific consensus described above, any regulatory scheme should also incorporate several additional general principles: first, the degree of regulatory scrutiny should be commensurate with the level of risk, keeping in mind the difference between real and perceived risk; second, similar things should be regulated in a similar way; and third, the scope of what requires regulatory review must make sense. These principles have been the premise for all Organisation for Economic Cooperation and Development (OECD; Paris) regulatory guidance documents since 1995 (refs. 29,30). They are further codified in the World Trade Organization (WTO; Geneva, Switzerland) Sanitary and Phytosanitary protection measures, to which WTO member states are bound[31]. If the scope of regulation (that is, 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 *ipso facto* is unscientific.

At least in theory, these science-based principles were embraced early on by US policymakers. In 1986, the US Office of Science and Technology Policy (OSTP; Washington, DC) published the "Coordinated Framework for the Regulation of Biotechnology." This policy statement called for oversight and regulatory triggers to focus on the risk-related characteristics of products, such as plants' weediness or toxicity, rather than on the process used for genetic modification[32].

That approach was reaffirmed in a 1992 federal 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."[9] 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. In practice, however, neither the US government nor any other government, except that of Canada, has adopted risk-based (that is, product-focused) regulatory frameworks.

The current US regulatory system

In the United States, no new legislation covering GE was enacted; instead, regulatory agencies extended the authority granted in previously existing laws to regulate GE plants as pesticides, plant pests, or noxious weeds[32].

The US EPA developed a concept called 'plant-incorporated protectants' (PIPs), defined as "substances plants produce for protection against pests, and the genetic material necessary to produce these substances," to capture GE crop plants under its legal authority to regulate pesticides[32,33]. All plants naturally produce compounds that are toxic to one pest or another, and these resistance traits are frequently enhanced, and new ones introduced, with classic breeding methods. But the agency applies its regulatory jurisdiction only if the PIP was introduced or enhanced by recombinant DNA technology. It is noteworthy that on the order of 99.99% of pesticidal substances found in our diet are intrinsic to foods[34]. If regulating naturally occurring pesticidal substances in plants is not necessary, it is not at all evident why strict regulation of all such substances introduced (or enhanced) should be needed.

The EPA's approach thus ignores any consideration of actual or potentially novel risk to human health or the natural environment. To sell plants that contain PIPs, sponsors must go through a process that is similar to the lengthy, complex and expensive process that applies to the licensing of chemical pesticides.

Moreover, under EPA regulations, what constitutes a 'pesticide' is defined by *intent*, rather than by any intrinsic properties of the product in question. Thus, any recombinant-DNA-mediated modification "intended for preventing, destroying, repelling, or mitigating any pest" (7 USC § 136) is treated as a pesticidal substance regardless of its potential to harm humans, other non-target organisms, or the environment. The result of this approach is that EPA requires the seeds of plants modified with molecular techniques to be regulated as pesticides and to bear labels indicating that the DNA from the transgene is the active pesticidal ingredient (**Fig. 1**).

Labeling of seeds as pesticides has had other unintended downstream consequences. For example, nurseries would have been reluctant to sell plum trees labeled as pesticides or to register themselves as pesticide-producing facilities if a more appropriate labeling and distribution procedure had not been developed by EPA (R. Scorza, personal communication). Corn seeds produced in winter nurseries in South America and shipped to the United States for spring planting have been stopped at the border for not having the appropriate Notice of Arrival of Pesticides and Devices. In February 2013, Pioneer Hi-Bred (now DuPont Pioneer; Johnston, IA) paid a $34,000 fine after 740 metric tons of seed were stopped at the border because the company had failed to file an appropriate Notice of Arrival for the shipment[35]. More recently, Pioneer had to pay $42,500 in civil penalties for paperwork violations[36].

The USDA's Animal and Plant Health Inspection Service (APHIS) created a similarly contrived rule for regulating GE crops under its legal authority. APHIS had long regulated the importation and interstate movement of plants and other organisms considered to be "plant pests," defined as living organisms "that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant

product" (7 USC § 7702). This approach is essentially binary: either a plant or other organism that an investigator might wish to introduce into the field is on the prohibited list of plants pests—and therefore requires a notification or permit—or it is exempt. This straightforward approach is nominally risk based in that the organisms required to undergo case-by-case governmental review are an enhanced-risk group—those that can actually injure or damage plants—compared with organisms not considered to be plant pests.

But although it is evident that an intact pathogen or other pest has the potential to harm agriculture, today it is scientifically indefensible to claim that any gene or DNA sequence from a pest would have the same effect. That was not a universal perspective in the late 1980s, when APHIS expanded the original concept of a plant pest to include every GE plant with even a snippet of DNA from a listed plant pest inserted with recombinant DNA techniques. Regulators invented a new category to encompass these plants: "regulated articles." The irony is that all crops are now known to contain naturally acquired plant-pathogen-derived sequences anyway[37,38].

Almost all GE plants field tested in the United States during the past three decades have included either a transfer DNA (T-DNA)-derived sequence from *Agrobacterium tumefaciens* or a 35S promoter sequence from cauliflower mosaic virus (CaMV); and both of these organisms are listed plant pests. Consequently, essentially every GE plant, even if its potential risk is obviously negligible, has been subject to review to rule out the possibility that inclusion of the pathogen-derived sequences may have transformed the modified plant into a plant pest, despite the scientific implausibility of such events.

Even if recombinant-DNA-modified plants do not include a DNA sequence from a listed plant or animal pest, USDA-APHIS has considered regulating recombinant organisms as "noxious weeds," which are broadly defined as "any plant or plant product that can directly or indirectly injure or cause damage to crops... livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment" (7 U.S.C. § 7702(10)). Like plant and animal pests, the cultivation of noxious weeds is generally subject to permitting, rigorous controls, or outright bans. As noxiousness is no more conditioned by snippets of DNA than are pesticidal properties, regulating GMOs by declaring them to be noxious weeds would compound the APHIS's current regulatory deficiencies.

In recent years, a growing number of GE plants have been produced without *A. tumefaciens* T-DNA, CaMV promoters or any other DNA sequence from a listed plant pest, thereby avoiding regulation under the plant pest classification. Critics have raised alarms about this supposed 'loophole' in APHIS's regulatory approach and the potential hazard of GE crops escaping meaningful oversight, even though most such products would still be regulated by the EPA and/or FDA[39].

Others have noted the inconsistencies generated by what they called a system that is "obsolete and an obstacle to the development of new agricultural products" and called for a re-evaluation of the current regulatory framework and the development of a "system that is based on science"—a view endorsed here—and which is exemplified by the approach described in Camacho *et al.*[40].

The Obama administration's review of biotech regulations described above provides an opportunity for needed changes. However, the needed changes must be in the direction of lessened coverage and regulatory burdens. Otherwise, the regulatory system will become even more antagonistic to science and to innovation for agriculture.

The FDA does not have a mandatory premarket review and approval process for foods derived from GE (or other) plants, but it did create a *de facto* approval requirement in the guise of a 'voluntary' consultation process for new foods from GE crops. The FDA 'requests' developers of GE crops to discuss with the agency whether foods derived from these crops are 'substantially equivalent' to foods from the same unmodified crops. If they are substantially equivalent, then FDA considers them as safe as their non-GE counterparts.

With the knowledge that the FDA has the authority to remove from commerce any foods it deems unsafe, developers of GE crops have in every case consulted with FDA, producing extensive documentation of each new product's safety and nutritional equivalency to a non-engineered reference food[41]. And without exception, the agency has determined that the foods approved to date are substantially equivalent (http://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon). However, even for products of negligible risk, some of these reviews have been unnecessarily prolonged: for example, 34 months in the case of non-browning Arctic apples containing rejiggered apple genes (apple polyphenol oxidase (PPO) genes *PPO2, GPO3, APO5* and pSR7 in the sense orientation under the control of a CaMV promoter) and 12 months for low-asparagine, bruise-resistant Innate potatoes containing engineered potato genes (two inverted repeats of fragments of the potato asparagine synthetase 1 (*Asn1*) and *Ppo5* genes and an inverted repeat fragment of the potato phosphorylase-L (*PhL*) and *R1* genes).

Regulating 'events'

GE plants are marked by an intended change—such as the introduction of herbicide tolerance or virus resistance—that is specifically tested for safety. Most GE events produce a protein or other metabolite(s) that can be tested for allergenicity and toxicity[42,43]. These methods are well established and widely accepted and will not be covered here.

Regulatory scrutiny is applied to individual 'transformation events' even when the same gene introduction has been evaluated many times previously, on the premise that the physical insertion of DNA into a genome could itself have hazardous, unintended effects by interfering with the normal functioning of endogenous genes[44]. The data indicate that such unintended changes are largely trait independent.

Consequently, each time a given gene is introduced into a plant, regulators consider that a new 'event' is created—even when copies of a single construct are inserted multiple times into different plants of the same species. Just as conventional breeders will often test thousands of genetic variants in the field to select the best individual plants for commercial development, it is necessary to produce hundreds, if not thousands, of unique events in the lab to obtain a single event or a small number of events that are further developed for commercial introduction (the 'lead event')[45,46]. But because each such event constitutes a unique product for the purposes of regulation, the field testing and marketing of any one of them requires the preparation of a unique data dossier and individual regulatory approval.

The case for retiring such regulatory requirements has been strengthened by experience. A review by Weber *et al.*[47] concluded that unintended DNA-level changes that could occur from GE are no different from those that occur in plant genomes naturally, a finding that was later substantiated in a review by Schnell *et al.*[13]. Likewise, Steiner *et al.*[26] observed that novel toxins not known to occur at the genus level have never been known to arise spontaneously during conventional breeding. These findings are consistent with the prediction of the 1989 National Research Council analysis: "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."

Of the many hundreds of thousands of plant varieties genetically improved with classic (pre-molecular) techniques that have been field tested, only a minuscule number (two, possibly three) have ever manifested any notable hazards for the environment, human health, or food safety. These exceptions listed by Steiner *et al.*[26] all involved toxins already known to be in the crop, not unknown toxins appearing *de novo*, and thus were predictable. Furthermore, the injuries resulting from these crops were minor ones, such as stomach aches or skin rashes. It must be emphasized that all were the result of conventional breeding, not modification by recombinant DNA technology or genome-editing techniques. That is why new varieties of plants that are known to harbor relatively high levels of toxins, such as potato, are customarily analyzed to ensure that levels of potentially harmful substances remain in the safe range, regardless of the technique used to modify them. (Many foods, including licorice and nutmeg, normally contain substances that can be toxic at high levels but are perfectly safe in the amounts routinely consumed. Others, such as kidney beans and cassava, contain harmful levels of toxins that are denatured by proper preparation and cooking.)

Changing the focus from conventional breeding to molecular breeding, the Commonwealth Scientific and Industrial Research Organization (CSIRO) of Australia developed a transgenic pea in 2006 that raised concerns about increased allergenicity. But this 2006 event occurred from the intended change (for which the breeders properly tested and withdrew the pea) and was not an unintended effect of the inserted genetic material[48]. Thus, even this 2006 CSIRO experience does not validate event regulation for unintended insertional effects, and a subsequent study indicates that withdrawing the transgenic pea may have been unnecessary anyway[49].

As in other forms of plant breeding, developers of recombinant DNA-modified plants typically screen hundreds or thousands of plants to identify candidates with the most desirable phenotypes[45]. As Bradford *et al.*[50] observe, "Conventional breeding programs generally evaluate populations with much wider ranges of phenotypic variation than is observed in transgenic programs." Therefore, no scientific justification exists for event-specific regulation of crops modified with recombinant DNA or gene-editing technology.

USDA regulators implicitly recognize the fact that event-specific regulation is generally unwarranted, as demonstrated by their 'extension' process, an expedited regulatory mechanism that can extend deregulation decisions to 'similar' crops. However, as of 31 July 2015, the USDA had used the extension process just 18 times out of the 116 Determinations of Nonregulated Status currently listed on its web site[51]. Only three of these had occurred since 2006, in part because companies petitioning for non-regulated status need to comply with regulatory requirements in foreign markets, which usually require full prior approval in the country of origin.

In the 24 years since the USDA's first deregulation of a GE crop, a vast amount of information on certain traits in certain crops has accumulated, and it is well established that there are no plant pest or noxious weed risks associated with already approved crop–gene combinations. Therefore, it is encouraging that the USDA recently announced it is reviewing its process for extending approvals[52]. This APHIS review will allow a reduction in regulatory burdens by extending a deregulation decision from an already deregulated crop to a sufficiently similar crop. However, this APHIS modification represents a minimal, inadequate reduction in regulatory burdens for three reasons.

First, APHIS is not creating a categorical exemption for the sufficiently similar crop but rather using Section 340.6(e) of its existing regulations to lighten the review process for sufficiently similar crops.

Second, using existing authority, APHIS explicitly states that each extension of non-regulated status is a "major federal action" that triggers the requirements of the National Environmental Policy Act (NEPA).

And third, by giving guidance for a lesser regulatory review for the extension of an already granted deregulation decision, APHIS falls far short of the fundamental reforms needed (for example, a tiered risk analysis similar to that proposed in this article).

Regardless, APHIS decisions in recent years appear to some observers to have been driven not by the imperative to conduct science-based risk assessment as the basis for timely decisions on approvals, but by the need imposed by USDA Office of General Counsel (USDA-OGC) to prepare a paper trail to safeguard against abusive, harassing procedural lawsuits under NEPA. That GMO approvals are even subject to NEPA highlights another target area ripe for, and in dire need of, regulatory reform.

Risk-based approaches to plant biotech regulation

A new approach to plant biotech regulation does not imply an unregulated environment. Rather, a new, truly risk-based approach would capture plants that require review and exempt those that do not. As in the past, there may be considerations related to environmental or food and feed safety.

The FDA's approach to 'New Plant Varieties'. One alternative to the current process-based approach that is directly applicable to GE products and that has been enshrined in federal policy for almost a quarter-century is the FDA's policy on 'Foods from New Plant Varieties[53]. Published in 1992, it emphasizes that the agency's Center for Food Safety and Applied Nutrition does not impose discriminatory regulation based on the use of one technique or another. Regulators exert greater scrutiny only when safety or nutrition-related issues exist, such as the presence of a completely new substance in the food supply,

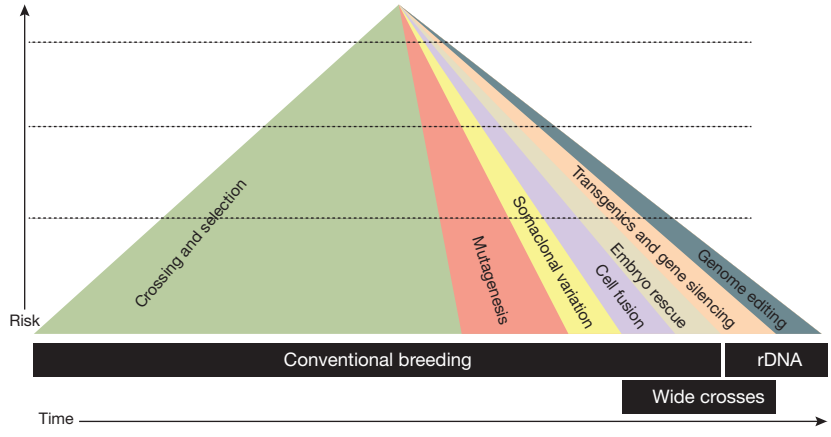

Figure 2 Different technologies have been implemented over history (time) in the plant breeding process. Each technology in turn can produce plants with different risk categories. These can be categorized vertically, as indicated by the dotted lines. The odds of a serious risk by any given method are very small. Adapted and updated from ref. 80.

	Risk			
Very high	Low	Moderate	High	High
High	Low	Low	Moderate	High
Low	Negligible	Low	Moderate	Moderate
Very low	Negligible	Negligible	Low	Moderate
	Marginal	Minor	Great	Major
	Harm			

Figure 3 Tabular algorithm used to classify GMOs into the Stanford Model environmental risk categories for regulatory purposes. The likelihood and harm categories, and the table, are adapted from ref. 58.

significant changes in a macronutrient, an increase in a natural toxicant or the presence of an allergen where a consumer would not expect it.

The 'Stanford Model'. The Stanford University Project on Regulation of Agricultural Introductions developed and described a widely applicable regulatory model for the environmental risk assessment of any organism, whatever the method or methods employed in its construction[2]. Its approach to assessing environmental and agricultural hazards and risks is patterned after the quarantine regulations of the USDA's Plant Protection Act, described above. The approach of the Stanford Model is to stratify plants into several risk categories, making the model more quantitative and nuanced than the USDA's long-standing approach to 'regulated articles' as plant pests or potential plant pests.

As shown in **Figure 2**, this universe can be divided in two ways: horizontally, according to risk categories, with higher risk toward the top of the pyramid; or by the oblique lines, which divide the universe of field trials according to technologies. The green area represents all field trials performed with plants created by conventional sexual breeding, such as selection or hybridization, progressing through tissue-culture-induced somaclonal variation, for example; and the tranches on the far right correspond to field trials with recombinant-DNA-modified and genome-edited plants.

Since the Stanford Model was published in 1997, scientific advances have offered newer methods of molecular breeding, known generally as genome editing or precision breeding and including ZFNs, TALENs, CRISPR-Cas9 and oligo-directed mutagenesis[54]. Whatever the technique(s) employed, the model continues to offer a scientifically defensible, risk-based regulatory approach that can be extended to synthetic biology as well.

The key point is that, when it comes to unintended effects, there is no special enrichment of risk associated with any particular technology used for genetic modification, and most modified plants pose little, if any, risk regardless of the modification method used. There are high-risk organisms—for example, foot-and-mouth disease virus, rusts that infect grains and highly invasive weeds—that require more caution in field tests, regardless of whether they are wild type or have been genetically modified in any way. Thus, there are high-risk organisms, but no high-risk techniques.

Plants may be noxious, invasive, toxic, etc., but most—domesticated crop plants in particular—are of negligible or low risk. Recombinant DNA technology and gene editing afford no particular monopoly on safety, but they are far more precise and their effects more predictable than is the case for the other, older techniques, leading to greater confidence about safety. Moreover, with recombinant technologies it is possible to test *in vitro*, *in vivo* and *in silico* the safety of the protein(s) expressed by the inserted genetic material.

The FDA defines 'genetic modification' in the 1992 policy statement on new plant varieties as "the alteration of the genotype of a plant using any technique, new or traditional"[53]. Thus, we use modification in a broad context to mean an alteration that results from adding, deleting or changing hereditary traits, irrespective of the method. Modifications may be minor, such as a single mutation that affects one gene, or major alterations of genetic material that affect many genes or even whole chromosomes. Most, if not all, cultivated food crops have been extensively genetically modified by one or more methods over time (as discussed above for maize and wheat).

The Stanford Model also resembles the approach that was taken by the NIH (Bethesda, MD) and Centers for Disease Control and Prevention (CDC; Atlanta, GA), as described in the handbook *Biosafety in Microbiological and Biomedical Laboratories*[55]. Now in its fifth edition, the handbook specifies the procedures and physical containment that are appropriate for research with microorganisms, including the most dangerous pathogens known. This handbook makes no distinction among organisms that are 'wild type' or that have been GE or GM by one or another of the classic or new breeding methods.

For the purposes of the handbook, microorganisms are stratified into risk categories by panels of expert scientists. Determinations of risk are based on such factors as the pathogenic characteristics of the organism, availability of treatment of infections, and physical factors (such as whether the organisms are grown under conditions that are likely to produce aerosols).

The Stanford Model similarly uses a series of risk categories that easily accommodate a wide spectrum of organisms and geographical regions, and even various regulatory agencies' preferences for more or less stringent regulation. It is able to evaluate any biological introduction, not just those that involve organisms modified by one technique or another. The need for such a broad approach is self evident, as severe ecological risks can be associated with often-ignored plant pests and 'exotic,' or non-coevolved, plants. However, recombinant-DNA-modified plants, which pose little risk, remain the focus of regulators' attention.

The appropriate risk category is a function solely of the intrinsic properties of the plant, the nature of any new or altered traits, and the environment into which the crop would be introduced.

The task of risk analysis starts with a determination of what needs to be protected from possible harm from the genetic modification, referred to as the object of protection[56]. With this clear objective in mind, the traits introduced (or enhanced) by the modification can be examined to determine whether they pose any incremental hazard to the entities to be protected. In each case, there must be a biologically plausible chain of events that could connect the modification to a harmful outcome and that can be described and tested by a hypothesis (i.e., a path to harm).

Beside food safety, which is evaluated separately, common protection goals include the prevention of enhanced weediness, loss of biodiversity from gene flow and harm to plants that are important to agriculture or ecosystems.

Too often, the focus of risk assessment has been on possible threats to biodiversity without consideration of possible benefits[57]. Threats to biodiversity include habitat destruction and degradation. One cause of such impacts on habitat has been the conversion of native lands to agriculture. Yet GE crops tend to increase yields on existing lands

and decrease the environmental footprint of production. These combine to reduce the pressure to convert additional lands to agriculture, thus acting to benefit biodiversity.

These risk-based factors are integral to any model algorithm for the approval of all plant introductions: first, the ability to become weedy or to cause cross-compatible relatives to become weedy; second, ecological relationships with other organisms that might be affected; and third, the ease or difficulty of mitigating any associated risks.

Risk then, is an arithmetic function of the *likelihood* that the genetic modification will lead to harm and the magnitude of the resulting harm, conventionally stated as:

Risk = Hazard × Exposure.

The *likelihood* can be classified into simple functional categories:

- Very low: expected to happen only in very rare cases;
- Low: expected in some cases;
- High: expected in many cases;
- Very high: expected in most cases.

The same is true for the *magnitude* of the harm, if harm were to materialize:

- Marginal: harm is negligible or too small to measure;
- Minor: harm is reversible and limited to a given time.

It is also true for the *period, space or population* affected:

- Great: harm can be widespread but is reversible;
- Major: harm is extensive, long-term, or permanent.

It then becomes possible to use these criteria to stratify plants: that is, to place a given plant into one of several risk categories (**Fig. 3**)[58]. Most common crop plant–gene combinations will belong in Category 1 (negligible risk), with only a few in Category 2 (low risk).

Location can also make a difference. Cotton could be in Category 1 if it were released outside its center of origin, and Category 2 if in

Box 1 Four case studies

In the box below, we present illustrations of risk assessment for different GE products. We work through four examples: herbicide-tolerant soybean; herbicide-tolerant sunflower or rice; virus-resistant squash; and insect-resistant sunflower. All of these assessments are for North America, where squash and sunflower are natives. Soybean and rice are not native, but rice has a weedy, cross-compatible relative nonetheless.

Herbicide-tolerant soybean:

- *Object of protection:* none obvious.
- *Likelihood of hazard:* very low—no sexually compatible or weedy relatives present.
- *Amount of harm:* marginal—herbicide resistance does not provide a selective advantage outside of agriculture.
- *Risk:* negligible.

Herbicide-tolerant sunflower or rice:

- *Object of protection:* diversity of wild sunflowers or rice.
- *Likelihood of hazard*: high, based on amount of known gene flow.
- *Amount of harm*: marginal—herbicide tolerance does not provide a selective advantage outside of agriculture.
- *Risk*: low.

Note that the worst-case scenario in herbicide-tolerant sunflower or rice would be that the farmer would be unable to use the herbicide any longer; thus, this is an herbicide market-protection (efficacy) issue rather than an environmental concern. In addition, the selection of herbicide-tolerant weeds might lead to greater herbicide use. However, that problem applies to all crop agriculture, not just GE-herbicide-tolerant crops. In any case, it behooves the technology providers to ensure that appropriate stewardship is applied to ensure longevity of the technology.

Virus-resistant (VR) squash:

- *Object of protection:* plants that might be outcompeted by wild squash.
- *Likelihood of hazard*: low or medium, based on amount of known gene flow.
- *Amount of harm*: marginal—virus resistance is not known to provide a selective advantage outside of agriculture.
- *Risk*: negligible.

GE squash varieties modified for resistance to cucumber mosaic virus (CMV), zucchini yellow mosaic virus (ZYMV) and watermelon mosaic virus (WMV) were deregulated in the United States in 1994. The USDA concluded in its environmental assessment that there was no evidence that gene flow would increase weediness or decrease diversity of the wild relatives, given that historic gene flow with improved, pest-resistant varieties has not done so previously even though breeders have already, in the course of decades, introduced several resistance traits in domesticated squash using conventional methods. Perhaps more importantly, CMV, ZYMV and WMV were not important in limiting the reproductive success of wild cucurbits, so the resistance traits would not be expected to increase weediness or invasiveness. Moreover, domesticated squash possess several traits that, if transferred to wild cucurbits, would reduce reproductive fitness, and hybrid plants are known to experience higher herbivory and bacterial disease, effectively canceling out any advantage in fitness from the transgenes[77]. Therefore, outcrossing from GE squash is unlikely to affect biodiversity in any meaningful way.

Insect-resistant (*Bt*) sunflower:

- *Object of protection:* wild sunflowers (and perhaps some endangered pollinator, should such an insect exist).
- *Likelihood of hazard:* high—cultivated and wild sunflower are known to hybridize easily, and insect pests have the potential to pose some limiting impact on reproductive success in wild plants. Thus, insect resistance could increase the competiveness or weediness of wild sunflower.
- *Amount of harm:* unknown.
- *Risk:* unknown.

In this case, risk assessment for *Bt* sunflower cannot be completed until certain knowledge gaps are addressed. One study[78] suggests that hybrids of wild and cultivated varieties can exhibit higher fecundity, but the extent and duration of this phenomenon remain unexplored[79].

Ultimately, most GE sunflowers would be Category 2 (low risk) if proposed for planting in the vicinity of wild populations. However, the *Bt* sunflower described above could be placed in a higher risk group—perhaps Category 3 (moderate risk)—unless either additional studies show that the insertion of a *Bt* gene does not confer a selective advantage to wild populations or effective confinement or control mechanisms become available to mitigate the risk.

Table 1 Categories of food risk posed by the introduction of various genes

Risk category	Description
Negligible	Marker genes, gene deletion, gene silencing (interruption or suppression of a gene using RNA interference or destruction of the coding sequence by genome editing) and genes that confer enhanced nutritional value. Given the extent to which RNA interference (RNAi)-mediated gene silencing occurs in nature, the current compositional analysis for transgenic plants is more than sufficient to ensure a high level of safety[62].
Low	The vast majority of transgenes introduced to date would fall into this category. They have been well characterized, and the safe use of their gene products as food and feed has been tested repeatedly in many instances in different crops, even though there is no indication so far that a given gene or protein behaves differently when moved to a different crop.
Intermediate	Bradford *et al.*[50] proposed this as a temporary category for genes encoding proteins that have not been thoroughly characterized. Once thoroughly characterized, the genes can be placed in an appropriate risk classification.
High	Genes that express proteins known to be allergenic or highly toxic to vertebrates and pharmaceuticals that are either active when orally ingested or poorly degraded by gastric fluids would present the highest risk. Genes that could increase the hazard posed by a plant, such as a gene that permits the hyperaccumulation of heavy metals in an edible plant, are another group that might be appropriate to this category.

the vicinity of its center of origin or when deployed near cross-compatible relatives. In the latter case, it is still necessary to assess the likely result of a transgene moving into wild relatives, such as whether it can provide them with a competitive advantage.

A salient characteristic of the model is that the factors taken into account are indifferent both to the nature of the genetic modification techniques employed, if any, and to the source(s) of the introduced genetic material. Whether conventional breeding techniques or molecular methods were used to modify an organism is irrelevant to the risk posed by that organism. The fact of DNAs being combined from phylogenetically distant organisms (i.e., organisms from different genera, families, orders, classes, phyla or kingdoms) is likewise irrelevant to the risk posed. Ultimately, any risk is rooted exclusively in the nucleotide base sequence of the exogenous DNA, and the overwhelming majority of such sequences are irrelevant to risk. The regulatory focus must therefore be on the phenotype.

Regulatory requirements are commensurate with risk. In a scientifically defensible, risk-based regulatory system, the measures required—by researchers and regulators—for compliance should be commensurate with the corresponding risk category. The level of oversight should increase as the level of risk does and should include the following: 'complete exemption' from regulatory review; a simple 'postcard notification' to a regulatory authority; 'premarket review of only the first product in a given category'; 'case-by-case review of all products in the category' (as with bona fide plant pests); or even 'prohibition' (as is the case currently for experiments with foot-and-mouth disease virus in the continental United States, for example).

Under such a system, some currently unregulated introductions of traditionally bred cultivars and so-called 'exotic' plants considered to be of moderate or greater risk would likely become subject to an appropriate level of regulatory review, as could plants with the newly introduced ability to synthesize a toxin at levels above thresholds of toxicological concern. Such a classification would take into account that the dose makes the poison, and that what is toxic to one organism (*Bt* protein to lepidoptera and coleoptera or chocolate to dogs) may be nontoxic or even highly desirable to another (chocolate to humans). But most recombinant-DNA-modified plants that now require case-by-case review would be subject to less (or no) regulatory scrutiny.

As implied above, the trait newly introduced or enhanced in the modified plant (or other organism) also needs to be considered. The introduction, enhancement or downregulation of most traits (for example, reduced levels of asparagine, which is converted to the presumptive carcinogen acrylamide at high temperatures) would add negligible or low risk and not alter the risk category. However, the introduction of a pest-resistance trait into a crop grown near sexually compatible wild relatives might raise the risk category if outcrossing of the trait could increase the reproductive fitness of wild plants and cause them to become weedy or invasive or could reduce the genetic diversity of wild populations. **Box 1** presents four case studies to illustrate the point for environmental risk.

The addition of genetic material about which there is minimal information might be considered of intermediate or uncertain risk, causing the modified plant to be placed in a higher risk category until further data indicates otherwise. Certain higher-risk traits, such as the ability to accumulate heavy metals or to synthesize toxins, allergens or orally active pharmaceuticals, would also elevate the risk category by one or more levels.

One final attribute of a science-based regulatory system is that it must base decisions on data and experience, and it must be able to adapt as new data and experience accumulate[59]. The approach of the Stanford Model implicitly incorporates this experiential adjustment.

Does the genetic change confer incremental risk? As mentioned above, proteins expressed by transgenes are tested for toxicity and allergenicity[60–62], and compositional analysis is performed to ensure nutritional equivalency[63,64]. A hallmark of crop plants is that their chemical composition can vary depending on the variety, but genetics is not the only source of variability in crops. Even in the absence of genetic modification, crops are notably affected by their environment and by agricultural practices. Thus, the composition of any given variety also depends on where and how it was grown[65]. Together, the genetic and varietal diversity in composition define the range that has been grown and consumed safely and that does not elicit undue safety concerns[66]. Significant deviations in composition are considered a sign of unintended changes[67].

Because it is conceivable that not all unintended changes might result in a detectable alteration in composition, animal feeding studies using whole food have sometimes been conducted in an attempt to detect any unintended, difficult-to-detect differences between GE food and a comparator. However, a European Food Safety Authority (Parma, Italy) study and others have concluded that such animal studies lack detection power[42,68]. These findings were further reinforced by the most recent report of the European Union's GMO Risk Assessment and Communication of Evidence (GRACE) project, which concluded that 90-day feeding trials do not provide any information above and beyond that provided by compositional analysis[43].

As discussed above, the probability of an unintended, undesirable change in GE plants is certainly no greater than in those created with conventional breeding and is extraordinarily low in both cases. As the 1989 NRC report observed, "With classical techniques of gene transfer. . . 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 plants modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression"[69].

Therefore, food and feed safety assessment should focus on the *intended* changes and levels of known toxicants in the species. Just as different crop plants pose different levels of environmental risk, the introduction of various genes can pose varying levels of food risk. These fit into easily delineated categories (**Table 1**)[50,70].

For most gene families, there is no justification for treating related proteins differently because, to conserve their function, proteins must conserve their character[62]. The case is illustrated in **Figure 4**, whereby distantly related (from a phylogenetic perspective) 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) proteins—the activity of which is blocked by the herbicide glyphosate—show the same overall three-dimensional structure. Thus, for example, if the native EPSPS from soybean is innocuous, so will be the similar CP4 version, or any other bacterial or plant version. As long as no EPSPS has evoked adverse reactions, all versions of EPSPS within the universe of EPSPS molecules should be recognized as substantially equivalent.

Enzymes are poorly tolerant of mutations that alter their three-dimensional structure—that is, their function or potential interactions with binding sites and/or other biomolecules can easily be disrupted. No amino acid substitutions, additions or deletions are known that convert an innocuous protein into a toxin or an allergen[71]. Additional introductions of these genes into food or feed crops, therefore, should be viewed as posing a very low risk.

Once the risk category of the parental organism and the incremental risk (if any) posed by the insertion (see above) are known, the investigator will be able to arrive at a 'final risk category' for the purposes of ascertaining to what regulatory requirements the field trial and/or commercialization would be subject.

If the insert is of negligible or low risk, it would not alter the risk category classification of the parental organism. If it is of intermediate risk, it would raise the risk category one level from that of the parental organism, and if the insert is of high risk, it would raise the risk classification by two levels. That final risk category would then dictate where on the spectrum of *exempt*, *notification*, *case-by-case review*, etc., the field trial or commercialization would fall and what actions (if any) for regulatory compliance were required.

The PIP classification. The EPA's PIP concept[33] is too artificial and contrived to have any relevance, beyond indicating that nontarget species need to be considered during risk evaluation. The lack of utility of the PIP classification is most evident in virus-resistant plants obtained using a gene(s) from the viruses that otherwise infect them, or when *cis* genes are used that could otherwise have been crossed in. There is simply no justification in data or experience for a regulatory classification of a PIP that singles out certain events for the same regulatory approach as if they were pesticides sprayed on crops[69]. Our opinion is that this classification should be eliminated.

Conclusions

Given the knowledge accumulated during the past two decades, it is evident that most of the regulatory regimes around the world, including those of the US EPA and USDA, are neither scientifically defensible nor justifiable: all too often, they lead to the plants of *lowest* risk being subject to the *highest* degree of scrutiny. The result is a massive waste of limited resources, huge disincentives to innovation in a time of great need and no increase in public or environmental safety.

As discussed above, there is no evidence that insertion of DNA into a genome via recombinant DNA technology leads to unique or incremental risks[13,71], nor is there any published evidence that insertion heterologous DNA insertions pose any unique risks. Compared with conventional breeding, the insertion of DNA via molecular techniques does not increase the probability of an adverse, unintended effect. And because risk is a function of the characteristics of the parental plant and the product of the inserted DNA, there is no justification for an independent, redundant review of food or feed safety for different events involving the same gene, regardless of the crop into which the gene is inserted[69].

An underappreciated impact of excessive regulation is that it disproportionately affects small enterprises and, especially, public research endeavors such as those at land-grant universities, which lack the necessary resources to comply with burdensome and costly regulatory requirements. Therefore, land-grant universities have been put at a substantial competitive disadvantage and are no longer able either to expose their students to state-of-the-art breeding programs or to deliver important new varieties to their constituencies.

The global regulatory compliance costs associated with an insect-resistant or herbicide-resistant recombinant DNA-modified variety of corn, for example, have been calculated to be as much as $35 million[72]. This cost estimate does not include the resources spent on products that are never approved; the costs borne by growers, shippers and processors associated with segregation, traceability and special labeling; or the opportunity costs of compliance with unnecessary regulation. Unfortunately, the global trend is toward increased regulatory oversight, so there is no end in sight to unnecessarily inflated regulatory costs.

Multinational corporate crop developers

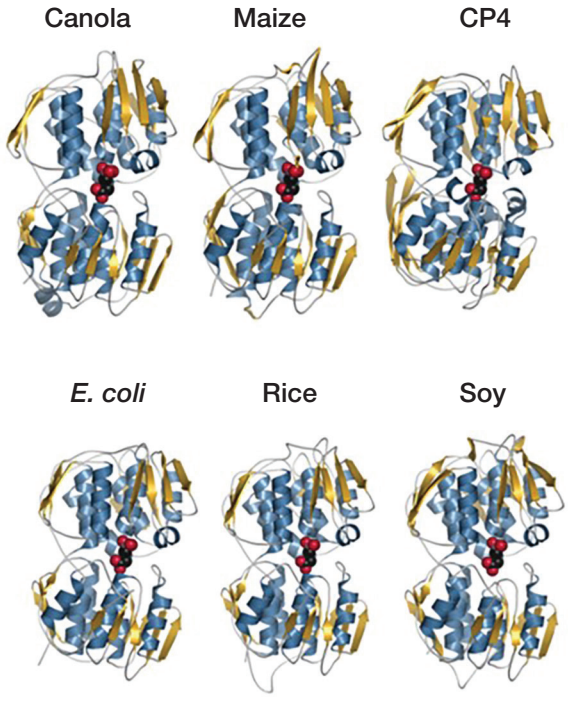

Figure 4 EPSPS from different plants and microbes. The *Escherichia coli* and soy CP4 crystal structures were used with the SwissModel to thread the canola, maize, rice, and native soy sequences onto the *E. coli* structure. The plant EPSPSs are related by >90 sequence identity to each other and by ~50% to the bacterial EPSPS. Helices are blue, strands are gold and the position of bound glyphosate (from the CP4 and *E. coli* structures) is modeled into each one. Figure courtesy of Joseph Jez, Washington University in St. Louis, with additional modifications.

can bear these high regulatory costs for high-value, huge-volume commodity crops, but only as long as global sales are large enough to justify the regulatory expenditures. With development costs so high, researchers in the public sector as well as those at nonprofit organizations and small startup companies rarely have sufficient resources to navigate the complex, expensive and uncertain regulatory approval process.

Under these circumstances, it is difficult to justify the expense of developing GE varieties of lower-market-value products, such as so-called specialty crops—fruits, nuts and vegetables—or (especially) the staple crops grown primarily by subsistence farmers in less developed countries. As a result, although numerous, promising laboratory and greenhouse experiments are conducted with GE fruits, vegetables, and such developing-world staples as millet, sorghum and cassava, the products most likely to advance through field testing to regulatory approval and commercialization are major commodity species, including corn, cotton, soy, canola, alfalfa and sugar beets[73,74].

There are other direct and indirect harms caused by unscientific and excessive regulation that circumscribes plants modified with molecular methods as a 'category' worthy of intensive scrutiny. Innovation of all sorts—including biopharming and biofortification, as well as the gradual, incremental improvements in crops that are typical of progress in agriculture—has been inhibited. Moreover, although this article focuses on plant breeding, the risk-based regulatory model we outline here could equally well apply to animals (fish, livestock and insects). Animal biotech is also in need of drastic regulatory reform[74].

As former US president Bill Clinton has noted, "The American people deserve a regulatory system that works for them, not against them: a regulatory system that protects and improves their health, safety, environment, and well-being and improves the performance of the economy without imposing unacceptable or unreasonable costs on society; regulatory policies that recognize that the private sector and private markets are the best engine for economic growth; regulatory approaches that respect the role of State, local, and tribal governments; and regulations that are effective, consistent, sensible, and understandable. We do not have such a regulatory system today.... In deciding whether and how to regulate, agencies should assess all costs and benefits of available regulatory alternatives, including the alternative of not regulating."[75]

Similar sentiments have been expressed by the current administration: "We share a fundamental desire for regulation and oversight that ensure the fulfillment of legitimate objectives, such as the protection of safety, health and the environment. Regulation and oversight should avoid unjustifiably inhibiting innovation, stigmatizing new technologies, or creating trade barriers."[76]

However, such lofty aspirations for regulation that is scientific, reasonable and public spirited are today the stuff of creative speechwriters, not regulatory reality. The current regulatory system fails to inspire confidence among consumers—as demonstrated by the growing demands for 'GMO-free' products—while keeping an estimated 90% or more of possible transgenic crops off the market.

A further shortcoming of existing process-based regulations is that they are always a step behind the introduction of new techniques. A case in point is the development of CRISPR-Cas9 and other genome-editing techniques, which have ignited intense debates on how best to regulate them. These pointless debates often focus on whether the organisms that result from modification with such techniques fall into pseudo-categories, such as GMOs, regulated articles or PIPs.

In contrast, the product-based protocol outlined here is capable of assessing any new risks that might be associated with genome editing—or for that matter the products of any other new technology that comes along in the future. Indeed, because the procedures describe here are based on risk-assessment principles that are independent of organism and traits, they can be applied to virtually any trait in any organism.

It is past time for regulatory reform that will begin to alleviate the public's misapprehensions and the excessive burdens on the research community by making regulation commensurate with the level of risk. Regulation must focus on the actual risks, which are presented by the end product of the modification and have nothing to do with the method used to achieve it. Moreover, regulation must be flexible and adapt as appropriate, to ensure that new technological tools can help to meet the rising global demand for sustainable food, feed, fiber and fuel.

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The authors declare competing financial interests: details are available in the online version of this paper (http://dx.doi.org/10.1038/nbt.3568).

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