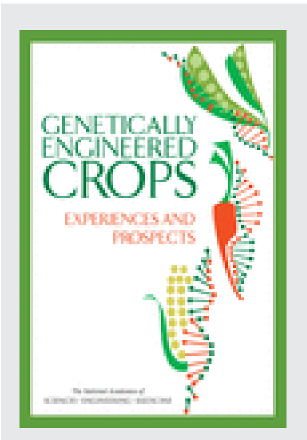

Genetically Engineered Crops: Experiences and Prospects

DETAILS

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AUTHORS

Committee on Genetically Engineered Crops: Past Experience and Future Prospects; Board on Agriculture and Natural Resources; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

Summary

Genetic engineering—a process by which humans introduce or change DNA, RNA, or proteins in an organism to express a trait or change the expression of an existing trait—was developed in the 1970s. Genetic improvement of crop varieties by the combined use of conventional breeding *and* genetic engineering holds advantages over reliance on either approach alone because some genetic traits that cannot be introduced or altered effectively by conventional breeding are amenable to genetic engineering. Other traits can be improved more easily with conventional breeding. Since the 1980s, biologists have used genetic engineering in plants to express many traits, such as longer shelf-life for fruit, higher vitamin content, and resistance to diseases.

For a variety of scientific, economic, social, and regulatory reasons, most genetically engineered (GE) traits and crop varieties that have been developed are not in commercial production. The exceptions are GE traits for herbicide resistance and insect resistance, which have been commercialized and sold in a few widely grown crops in some countries since the mid-1990s. Available in fewer than 10 crops as of 2015, varieties with GE herbicide resistance, insect resistance, or both were grown on about 12 percent of the world's planted cropland that year (Figure S-1). The most commonly grown GE crops in 2015 with one or both of those traits were soybean (83 percent of land in soybean production), cotton (75 percent of land in cotton production), maize (29 percent of land in maize production), and canola (24 percent of land in canola production) (James, 2015). A few other GE traits—such as resistance to specific viruses and reduction of browning in the flesh of apples and potatoes—had been incorporated into some crops in commercial production in 2015, but these GE crops were produced on a relatively small number of hectares worldwide.

The Committee on Genetically Engineered Crops: Past Experience and Future Prospects was charged by the Academies to use evidence accumulated over the last two decades for assessing the purported negative effects and purported benefits of GE crops and their accompanying technologies (see the committee's statement of task in Box S-1). Given the small number of commercialized traits and the few crops into which they have been incorporated, the data available to the committee were restricted mostly to those on herbicide resistance and insect resistance in maize, soybean, and cotton. The data were also restricted geographically in that only a few countries have been growing these crops for a long period of time.

Many claims of beneficial and adverse agronomic, environmental, health, social, and economic effects of GE crops have been made. The committee devoted Chapters 4 through 6 of its report to the available evidence related to claims of the effects of GE crops in the literature or presented to the committee by invited speakers and in submitted comments from members of the public. Findings and recommendations on those effects are summarized below in the section "Experiences with Genetic Engineering."

The committee was also tasked with exploring emerging methods in genetic engineering as they relate to agriculture. Newer approaches to changing an organism's genome—such as genome editing, synthetic biology, and RNA interference—were becoming more relevant to agricultural crops at the time the committee was writing its report. A few crops in which a trait was changed by using at least one of those approaches, such as the nonbrowning apple, were approved in 2015 for production in the United States. Those approaches and examples of how they may be used in the future to change traits in agricultural crops are described in Chapters 7 and 8, and the committee's findings and conclusions are in the "Prospects for Genetic Engineering" section of this summary.

FIGURE S-1 Type and location of commercially grown genetically engineered (GE) crops in 2015.[1] NOTE: In 2015, almost 180 million hectares of GE crops were planted globally. Over 70 million hectares were planted in the United States. GE crops produced in Brazil, Argentina, India, and Canada accounted for over 90 million hectares. The remaining hectares of GE crops were spread among 23 countries.

[1]Adapted from James, C. 2014. Global Status of Commercialized Biotech/GM Crops: 2014. Ithaca, NY: International Service for the Acquisition of Agri-biotech Applications, and James, C. 2015. Global Status of Commercialized Biotech/GM Crops: 2015. Ithaca, NY: International Service for the Acquisition of Agri-biotech Applications.

BOX S-1 Statement of Task

Building on and updating the concepts and questions raised in previous National Research Council reports addressing food safety, environmental, social, economic, regulatory, and other aspects of genetically engineered (GE) crops, and with crops produced using conventional breeding as a reference point, an ad hoc committee will conduct a broad review of available information on GE crops in the context of the contemporary global food and agricultural system. The study will:

- Examine the history of the development and introduction of GE crops in the United States and internationally, including GE crops that were not commercialized, and the experiences of developers and producers of GE crops in different countries.
- Assess the evidence for purported negative effects of GE crops and their accompanying technologies, such as poor yields, deleterious effects on human and animal health, increased use of pesticides and herbicides, the creation of "super-weeds," reduced genetic diversity, fewer seed choices for producers, and negative impacts on farmers in developing countries and on producers of non-GE crops, and others, as appropriate.
- Assess the evidence for purported benefits of GE crops and their accompanying technologies, such as reductions in pesticide use, reduced soil loss and better water quality through synergy with no-till cultivation practices, reduced crop loss from pests and weeds, increased flexibility and time for producers, reduced spoilage and mycotoxin contamination, better nutritional value potential, improved resistance to drought and salinity, and others, as appropriate.
- Review the scientific foundation of current environmental and food safety assessments for GE crops and foods and their accompanying technologies, as well as evidence of the need for and potential value of additional tests. As appropriate, the study will examine how such assessments are handled for non-GE crops and foods.
- Explore new developments in GE crop science and technology and the future opportunities and challenges those technologies may present, including the R&D, regulatory, ownership, agronomic, international, and other opportunities and challenges, examined through the lens of agricultural innovation and agronomic sustainability.

In presenting its findings, the committee will indicate where there are uncertainties and information gaps about the economic, agronomic, health, safety, or other impacts of GE crops and food, using comparable information from experiences with other types of production practices, crops, and foods, for perspective where appropriate. The findings of the review should be placed in the context of the world's current and projected food and agricultural system. The committee may recommend research or other measures to fill gaps in safety assessments, increase regulatory clarity, and improve innovations in and access to GE technology.

The committee will produce a report directed at policymakers that will serve as the basis for derivative products designed for a lay audience.

The committee conducted its work at a time during which the genetic-engineering approaches that had been in use when national and regional regulatory systems were first developed were being replaced with newer approaches that did not fit easily into most regulatory systems or even into some older definitions of the term *genetically engineered*. That state of transition made the committee's charge to review the scientific foundation of environmental and food-safety assessments both timely and challenging. In Chapter 9, the committee undertook a thorough review of regulatory systems in the United States, the European Union, Canada, and Brazil as examples of diverse regulatory approaches. Political and cultural priorities in a society often influence how regulatory regimes are structured. In practice, some regimes place more emphasis on the process used to change the genome than do others. As the approaches to genetic engineering of crops change, some regulatory regimes may not be equipped to regulate traits introduced with newer approaches. The committee found that to be the case for the existing regulatory regime in the United States.

The committee avoided sweeping, generalized statements about the benefits or adverse effects of GE crops, concluding that, for a number of reasons, such statements are not helpful to the policy conversation about GE crops. First, genetic engineering has had and continues to have the potential to introduce many traits into agricultural crops; however, only two traits—insect resistance and herbicide resistance—have been used widely. Claims about the effects of existing GE crops frequently assume that the effects of those two traits apply to potential effects of the genetic-engineering process generally; however, different traits probably have different effects. For instance, a GE trait that alters the nutritional content of a crop would most likely not have the same environmental or economic effects as GE herbicide resistance. Second, not all existing GE crops contain both insect resistance and herbicide resistance. For example, at the time the committee was writing its report, GE soybean in the United States had GE resistance to a herbicide and no resistance to insects, and GE cotton in India had resistance to insects but no resistance to herbicides. The agronomic, environmental, and health effects of those two traits are different, but the distinction is lost if the two are treated as one entity. Third, effects of a single crop-trait combination can depend on the species of insects or weeds present in the field and their abundance, the scale of production, a farmer's access to seeds and credit, the availability of extension services to the farmer, and government farm policies and regulatory systems.

Finally, sweeping statements are problematic because the formation of policies for GE crops involves not just technical risk assessment but legal issues, economic incentives, social institutions and structures, and diverse cultural and personal values. Indeed, many claims about GE crops presented to the committee were about the appropriateness of legal or social strategies pursued by parties inside and outside governments to permit or restrict GE crop development and production. The committee carefully examined the literature and the information presented to it in search of evidence regarding those claims.

THE COMMITTEE'S PROCESS

Assessment of risks and benefits associated with a technology is often considered to involve analysis of the scientific literature and expert opinion on the technology to underlie a set of statistically supported conclusions and recommendations. In 1996, however, the National Research Council broke new ground on risk assessment with the highly regarded report *Understanding Risk: Informing Decisions in a Democratic Society.* That report pointed out that a purely technical assessment of risk could result in an analysis that accurately answered the wrong questions and was of little use to decision makers.[2] It outlined an approach that balanced analysis and deliberation in a manner more likely to address the concerns of interested and affected parties in ways that earned their trust and confidence. Such an analytic-deliberative approach aims at getting broad and diverse participation so that the right questions can be formulated and the best, most appropriate evidence for addressing them can be acquired.

The Academies study process requires that, in all Academies studies "efforts are made to solicit input from individuals who have been directly involved in, or who have special knowledge of, the problem under consideration"[3] and that the "report should show that the committee has considered all credible views on the topics it addresses, whether or not those views agree with the committee's final positions. Sources must not be used selectively to justify a preferred outcome."[4] The finding of the 1996

[2]National Research Council. 1996. Understanding Risk: Informing Decisions in a Democratic Society. Washington, DC: National Academies Press.

[3]For more information about the Academies study process, see http://www.nationalacademies.org/studyprocess/. Accessed July 14, 2015.

[4]Excerpted from "Excellence in NRC Reports," a set of guidelines distributed to all committee members.

National Research Council report and the Academies requirements were of special importance in dealing with GE crops and foods, given the diverse claims about the products of the technology.

To develop a report addressing the statement of task, 20 persons in diverse disciplines were recruited to the committee on the basis of nominations and of the need for a specific mix of expertise. In the information-gathering phase of the study, the committee heard from 80 presenters who had expertise in a variety of topics and from persons who had a broad array of perspectives regarding GE crops.[5] Input from the public was also encouraged via open meetings and through a website. Over 700 documents and comments were received through the website and were read by the committee and staff. The committee has responded to the comments in this report and has made its responses widely accessible through its website.

EXPERIENCES WITH GENETIC ENGINEERING

The experiences with genetic engineering in agriculture that the committee evaluated were related primarily to crops with GE herbicide resistance, insect resistance, or both. The committee's assessment of the available evidence on agronomic, environmental, health, social, and economic effects led to the following findings and recommendations.

Agronomic and Environmental Effects

The committee examined the effects of GE insect resistance on crop yield, insecticide use, secondary insect-pest populations, and the evolution of resistance to the GE trait in targeted insect populations. It looked at the effects of GE herbicide resistance on crop yield, herbicide use, weed-species distribution, and the evolution of resistance to the GE trait in targeted weed species. The committee also investigated the contributions to yield of genetic engineering versus conventional breeding and reviewed the effects of GE crops on biodiversity within farms and at the landscape and ecosystem levels.

The incorporation of specific modified genes from the soil bacterium *Bacillus thuringiensis* (*Bt*) into a plant genome via genetic engineering results in production of a *Bt* protein that, when ingested, disrupts cells in the target insect's digestive system, resulting in death. There are many *Bt* proteins, and more than one may be incorporated into a crop to target different insect species or to guard against insects that evolve resistance to a *Bt* toxin.

The committee examined results of experiments conducted on small plots of land that compared yields of crop varieties with *Bt* to yields of similar varieties without *Bt*. It also assessed surveys of yield on large- and small-scale farms in a number of countries. It found that *Bt* in maize and cotton from 1996 to 2015 contributed to a reduction in the gap between actual yield and potential yield (Figure S-2) under circumstances in which targeted pests caused substantial damage to non-GE varieties and synthetic chemicals could not provide practical control.

In the experimental plot studies in which the *Bt* and non-*Bt* varieties were not true isolines,[6] differences in yield may have been due to differences in insect damage or other characteristics of the varieties that affect yield, so there could be underestimates and overestimates of the contribution of the *Bt* trait itself. In the surveys of farmers' fields, reported differences in yield between *Bt* and non-*Bt* varieties may be due to differences between the farmers who plant and do not plant the *Bt* varieties. The differences could inflate the apparent yield advantage of the *Bt* varieties if *Bt*-adopting farmers on the average have other production advantages over those who do not adopt the technology.

[5]These presentations were recorded and can be viewed at http://nas-sites.org/ge-crops/.
[6]Isolines = individuals that differ genetically from one another by only a small number of genetic loci.

In areas of the United States and China where adoption of either *Bt* maize or *Bt* cotton is high, there is statistical evidence that some insect-pest populations are reduced regionally and that this benefits both adopters and nonadopters of *Bt* crops. In some midwestern states, a once important pest, the European corn borer, has become so uncommon since the introduction of *Bt* maize that the current presence of the *Bt* toxin for this insect in most of the maize in the Midwest is not economically warranted, yet its use will continue selection of *Bt*-resistant European corn borers.

The evidence showed decreased spraying of synthetic insecticides on *Bt* maize and cotton, and the use of *Bt* crop varieties in some cases has been associated with lower use of insecticides in non-*Bt* varieties of the crop and other crops. Some secondary (nontargeted) insect pests have increased in abundance, but in only a few cases has the increase posed an agronomic problem. Target insects have been slow to evolve resistance to *Bt* proteins in the United States when the government-mandated regulatory strategy required *Bt* plants to contain a high enough dose of *Bt* protein to kill insects that have partial genetic resistance to the toxin. That regulatory strategy also required the maintenance of non-*Bt* varieties of the crop, called refuges, in or near the farmer's field with the *Bt* varieties so that a percentage of the insect population that is susceptible to the toxin is not exposed to the *Bt* protein, survives, and mates with the rare resistant individuals that survived on the *Bt* variety. The committee found that this high dose/refuge strategy appeared to be successful in delaying the evolution of resistance to *Bt* in target insects; however, resistance to *Bt* in target insects has occurred on U.S. and non-U.S. farms where high doses were not used or refuges were not maintained. For example, resistance of pink bollworm to two *Bt* toxins expressed in GE cotton is widespread in India.

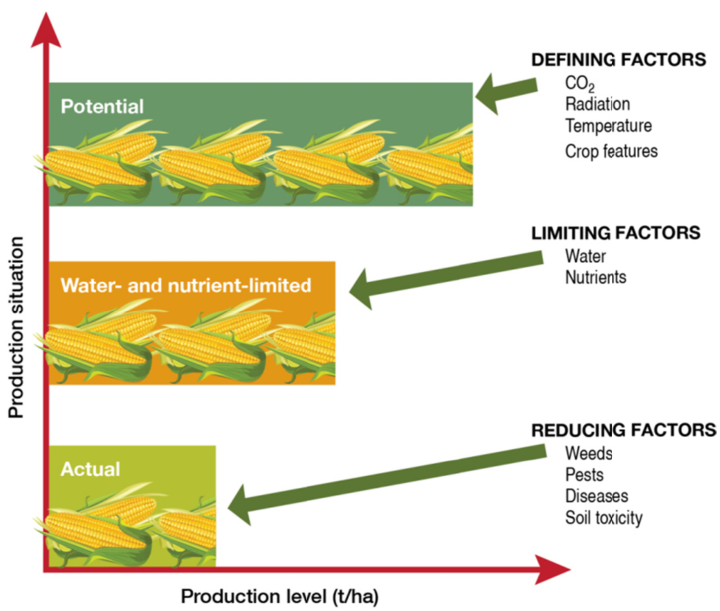

FIGURE S-2 Factors that determine crop yield.[7] NOTE: Potential yield is the theoretical yield that a crop genotype can achieve without any limitations of water or nutrients and without losses to pests and disease, given a specified carbon-dioxide concentration, temperature, and incident photosynthetically active radiation. Limitations of natural nutrient and water availability cause gaps between the potential yield and actual yield if nutrient supplementation and water supplementation are not possible. Actual yield may be further curtailed by "reducing factors": insect pests and diseases, which physically damage crops; weeds, which reduce crop growth by competition for water, light, and nutrients; and toxicity caused by waterlogging, soil acidity, or soil contamination.

[7]Based on van Ittersum, M.K., K.G. Cassman, P. Grassini, J. Wolf, P. Tittonell, and Z. Hochman. 2013. Yield gap analysis with local to global relevance–a review. Field Crops Research 143:4–17.

Herbicide-resistance traits allow a crop to survive the application of a herbicide that would otherwise kill it. The herbicide is applied to a field with a herbicide-resistant crop to control weeds susceptible to that herbicide. Studies of GE herbicide-resistant crops indicate that herbicide resistance contributes to higher yield where weed control is improved because of the effectiveness of the specific herbicide used in conjunction with the herbicide-resistant crop. With regard to changes in the amount of herbicide used since the commercialization of GE crops, the committee found that there were decreases in total kilograms of herbicide applied per hectare of crop per year when herbicide-resistant crops were first adopted, but the decreases have not generally been sustained. Although total kilograms of herbicide applied per hectare is often referred to in assessments of changes in risks to the environment or to human health due to GE crops, this measurement is uninformative because the environmental and health hazards of different herbicides vary, so the relationship between kilograms of herbicide applied per hectare and risk is poor.

Strategies to delay the evolution of pest resistance differ between herbicide-resistant and insect-resistant crops. *Bt* is always present in an insect-resistant crop, whereas the herbicide-resistant trait selects for weed resistance only if the corresponding herbicide is applied to the field. Weeds exposed repeatedly to the same herbicide are likely to evolve resistance to it. Therefore, delaying the evolution of resistance in weeds in fields of herbicide-resistant crops requires diverse weed-management strategies. The committee found that in many locations some weeds had evolved resistance to glyphosate, the herbicide to which most GE crops were engineered to be resistant. Resistance evolution in weeds could be delayed by the use of integrated weed-management approaches, especially in cropping systems and regions where weeds have not yet been exposed to continuous glyphosate applications. However, the committee recommended further research to determine better approaches for management of resistance in weeds.

Some weeds are more susceptible to particular herbicides than others. In locations where glyphosate is used extensively, weed species that are naturally less susceptible to it may populate a field. The committee found evidence of such shifts in weed species but little evidence that agronomic harm had resulted from the change.

There is disagreement among researchers about how much GE traits can increase yields compared with conventional breeding. In addition to assessing detailed surveys and experiments comparing GE with non-GE crop yields, the committee examined changes over time in overall yield per hectare of maize, soybean, and cotton reported by the U.S. Department of Agriculture (USDA) before, during, and after the switch from conventional to GE varieties of these crops. No significant change in the rate at which crop yields increase could be discerned from the data. Although the sum of experimental evidence indicates that GE traits are contributing to actual yield increases, there is no evidence from USDA data that they have substantially increased the rate at which U.S. agriculture is increasing yields.

The committee examined studies that tested for changes in the abundance and diversity of insects and weeds in GE cropping systems and in the diversity of types of crops planted and the genetic diversity within each crop species. On the basis of the available data, the committee found that planting of *Bt* crops has tended to result in higher insect biodiversity on farms than planting similar varieties without the *Bt* trait that were treated with synthetic insecticides. At least in the United States, farmers' fields with herbicide-resistant GE maize and soybean sprayed with glyphosate have weed biodiversity similar to that in fields with non-GE crop varieties, although there were differences in abundance of some specific weed species.

Since 1987, there has been a decrease in diversity of crops grown in the United States—particularly in the Midwest—and a decrease in frequency of rotation of crops. However, the committee could not find studies that tested for a cause-and-effect relationship between the use of GE crops and this pattern. The committee noted that maize could be more easily grown without rotation in some areas if it expressed a *Bt* toxin targeted for corn rootworm. Changes in commodity prices might also be responsible for decreases in rotation. The data do not indicate that genetic diversity among major crop varieties has declined since 1996 after the widespread adoption of GE crops in some countries. That does not mean that declines in diversity among crop varieties and associated organisms will not occur in the future.

Overall, the committee found no conclusive evidence of cause-and-effect relationships between GE crops and environmental problems. However, the complex nature of assessing long-term environmental changes often made it difficult to reach definitive conclusions. That is illustrated by the case of the decline in overwintering monarch butterfly populations. Studies and analyses of monarch dynamics reported as of March 2016 have not shown that suppression of milkweed by glyphosate is the cause of monarch decline. However, there is as yet no consensus among researchers that increased glyphosate use is not at all associated with decreased monarch populations. Overwintering monarch populations have increased moderately in the last 2 years. Continued monitoring will be useful.

Recommendations on Agronomic and Environmental Effects:

- To assess whether and how much current and future GE traits themselves contribute to overall farm yield changes, research should be conducted that isolates effects of the diverse environmental and genetic factors that contribute to yield.
- In future experimental survey studies that compare crop varieties with *Bt* traits and those varieties without the traits, it is important to assess how much of the difference in yield is due to decreased insect damage and how much may be due to other biological or social factors.
- Given the theoretical and empirical evidence supporting the use of the high dose/refuge strategy for *Bt* crops to delay the evolution of resistance, development of crop varieties without a high dose of one or more toxins should be discouraged and planting of appropriate refuges should be incentivized.
- Seed producers should be encouraged to provide farmers with high-yielding crop varieties that have only the pest-resistance traits that are appropriate for their region and farming situation.
- Because of the difference in toxicity in the various chemicals used, researchers should be discouraged from publishing data that simply compare total kilograms of herbicide used per hectare per year because such data can mislead readers.
- To delay evolution of resistance to herbicides in places where GE crops with more than one herbicide-resistance trait are grown, integrated weed-management approaches beyond simply spraying mixtures of herbicides are needed. That will require effective extension programs and incentives for farmers.
- Although multiple strategies can be used to delay weed resistance, there is insufficient empirical evidence to determine which strategy is expected to be most effective in a given cropping system. Therefore, research at the laboratory and farm level should be funded to improve strategies for management of resistance in weeds.

Human Health Effects

The committee heard presenters and received public comments voicing concern about the safety of foods derived from GE crops. It also received and reviewed several peer-reviewed reports that concluded that there is no evidence of health risks. To assess the presented claims, the committee first examined the testing procedures used to evaluate the safety of GE crops. It then looked for evidence supporting or refuting claims related to specific health effects. The committee makes clear in its report that there are limits to what can be known about the health effects of any food, whether it is produced through conventional breeding alone or in conjunction with genetic engineering. Acute effects are more straightforward to assess than long-term chronic effects.

Testing of GE crops and food derived from GE crops falls into three categories: animal testing, compositional analysis, and allergenicity testing and prediction. Animal testing typically involves rodents that are divided into treatment groups fed either GE or non-GE food. Current internationally accepted animal-testing protocols use small samples with restricted statistical power, so they might not detect real differences between treatments or might result in statistically significant results that are not biologically relevant. Although the design and analysis of many animal-feeding studies were not optimal, the committee's examination of the large group of experimental studies available provided sufficient evidence that animals were not harmed by eating food derived from GE crops. In addition to experimental data, analysis of long-term data on the health and feed-conversion efficiency of livestock spanning a period of time before and after the introduction of GE crops found no adverse effects on these measures associated with the feeding of GE crops to livestock.

As part of the regulatory process to establish that GE crops are substantially equivalent to non-GE crops, GE crop developers submit comparative data on the nutrient and chemical composition of their GE plant compared with a similar (isoline) variety of the crop. Statistically significant differences in nutrient and chemical composition have been found between GE and non-GE plants by using traditional methods of compositional analysis, but the differences have been considered to fall within the range of naturally occurring variation found in currently available non-GE crops. Newer approaches that involve transcriptomics, proteomics, and metabolomics are beginning to be used by researchers to assess compositional differences. In most cases examined, the differences found in comparisons of transcriptomes, proteomes, and metabolomes in GE and non-GE plants have been small relative to the naturally occurring variation found in non-GE crop varieties that is due to genetics and environment. If an unexpected change in composition beyond the natural range of variation in conventionally bred crop varieties were present in a GE crop, -omics technologies would be more likely than current methods to find the difference, but differences in composition found by using -omics methods do not, on their own, indicate a safety problem.

Assessment of potential allergenicity of a food or food product from a GE crop is a special case of food toxicity testing and is based on two scenarios: transfer of any protein from a plant known to have food-allergy properties and transfer of any protein that could be a de novo allergen. No animal model exists for predicting sensitization to food allergens. Therefore, researchers have relied on multiple indirect methods for predicting whether an allergic response could be caused by a protein that either is intentionally added to a food by genetic engineering or appears in a food as an unintended effect of genetic engineering. Endogenous protein concentrations with known allergic properties also have to be monitored because it is possible that their concentration could change as a result of genetic engineering.

To identify the transfer of a potential allergen, a standardized testing approach is recommended that determines whether the newly expressed protein is similar to a protein already known to be an allergen. If it is, the expressed protein becomes suspect and should be tested in people with an allergy to the related protein. If it is not similar to a known allergen but is not digested by simulated gut fluids, it could be a novel food allergen; this conclusion comes from research demonstrating that proteins already known to be food allergens are resistant to digestion by gut fluids. The committee noted that a substantial proportion of people do not have highly acidic gut fluids, and the simulated gut-fluid test may not be efficient for such people. For endogenous allergens in a crop, it is helpful to know the range of allergen concentrations in a broad set of varieties grown in a variety of environments, but it is most important to know whether adding the GE crop to the food supply will change the general exposure of humans to the allergen. Testing for allergenicity before commercialization could miss allergens to which the population had not previously been exposed, so post-commercialization allergen testing would be useful in ensuring that consumers are not exposed to allergens, but the committee recognizes that such testing would be difficult to conduct.

The committee received a number of comments from people concerned that GE food consumption may lead to higher incidence of specific health problems including cancer, obesity, gastrointestinal tract illnesses, kidney disease, and such disorders as autism spectrum and allergies. There have been similar hypotheses about long-term relationships between those health problems and changes in many aspects of the environment and diets, but it has been difficult to generate unequivocal data to test these hypotheses. To address those hypotheses with specific regard to GE foods in the absence of long-term, case-controlled studies, the committee examined epidemiological time-series datasets from the United States and Canada, where GE food has been consumed since the mid-1990s, and similar datasets from the United Kingdom and western Europe, where GE food is not widely consumed. The epidemiological data on some specific health problems are generally robust over time (for example, cancers) but are less reliable for others. The committee acknowledges that the available epidemiological data include a number of sources of bias.

The committee found no evidence of differences between the data from the United Kingdom and western Europe and the data from the United States and Canada in the long-term pattern of increase or decrease in specific health problems after the introduction of GE foods in the 1990s. More specifically, the incidences of a variety of cancer types in the United States and Canada have changed over time, but the data do not show an association of the changes with the switch to consumption of GE foods. Furthermore, patterns of change in cancer incidence in the United States and Canada are generally similar to those in the United Kingdom and western Europe, where diets contain much lower amounts of food derived from GE crops. Similarly, available data do not support the hypothesis that the consumption of GE foods has caused higher rates of obesity or type II diabetes or greater prevalence of chronic kidney disease in the United States. Celiac-disease detection began increasing in the United States before the introduction of GE crops and the associated increased use of glyphosate; the disease appears to have increased similarly in the United Kingdom, where GE foods are not typically consumed and glyphosate use did not increase. The similarity in patterns of increase in autism spectrum disorder in children in the United States and the United Kingdom does not support the hypothesis of a link between eating GE foods and the prevalence of the disorder. The committee also did not find a relationship between consumption of GE foods and the increase in prevalence of food allergies.

With regard to the gastrointestinal tract, the committee determined, on the basis of available evidence, that the small perturbations sometimes found in the gut microbiota of animals fed foods derived from GE crops are not expected to cause health problems. Understanding of this subject is likely to improve as the methods for identifying and quantifying gut microorganisms mature. On the basis of its understanding of the process required for horizontal gene transfer from plants to animals and data on GE organisms, the committee concludes that horizontal gene transfer from GE crops or non-GE crops to humans is highly unlikely and does not pose a health risk. Experiments have found that *Bt* gene fragments—but not intact *Bt* genes—can pass into organs and that these fragments present concerns no different from those posed by other genes that are in commonly consumed non-GE foods and that pass into organs as fragments. There is no evidence that *Bt* transgenes or proteins are found in the milk of ruminants. Therefore, the committee finds that consuming dairy products should not lead to exposure to *Bt* transgenes or proteins.

There is ongoing debate about potential carcinogenicity of glyphosate in humans. In 2015, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) issued a monograph in which it changed its classification of glyphosate from Group 2B (possibly carcinogenic to humans) to Group 2A (probably carcinogenic to humans). However, the European Food Safety Authority evaluated glyphosate after the IARC report was released and concluded that glyphosate is unlikely to pose a carcinogenic risk to humans. Canada's health agency found that current food and dermal exposure to glyphosate, even in those who work directly with it, is not a health concern as long as it is used as directed in product labels. The U.S. Environmental Protection Agency (EPA) found that glyphosate does not interact with estrogen, androgen, or thyroid systems. Thus, there is disagreement among expert committees on the potential health harm that could be caused by the use of glyphosate on GE crops and in other applications. Analyses to determine the health risk posed by glyphosate and formulations that include it must take marginal exposure into account.

On the basis of its detailed examination of comparisons between currently commercialized GE and non-GE foods in compositional analysis, acute and chronic animal toxicity tests, long-term data on health of livestock fed GE foods, and epidemiological data, the committee concluded that no differences have been found that implicate a higher risk to human health safety from these GE foods than from their non-GE counterparts. The committee states this finding very carefully, acknowledging that any new food—GE or non-GE—may have some subtle favorable or adverse health effects that are not detected even with careful scrutiny and that health effects can develop over time.

Recommendations on Human Health Effects:

- Before an animal test is conducted, it is important to justify the size of a difference between treatments in each measurement that will be considered biologically relevant.
- A power analysis based on within treatment standard deviations found in previous tests should be done whenever possible to increase the probability of detecting differences that would be considered biologically relevant.
- In cases in which early published studies produce equivocal results regarding health effects of a GE crop, follow-up experimentation using trusted research protocols, personnel, and publication outlets should be used to decrease uncertainty and increase the legitimacy of regulatory decisions.
- Public funding in the United States should be provided for independent follow-up studies when equivocal results are found in reasonably designed initial or preliminary experimental tests.
- There is an urgent need for publicly funded research on novel molecular approaches for testing future products of genetic engineering so that accurate testing methods will be available when the new products are ready for commercialization.

Social and Economic Effects

The committee examined evidence on claims associated with social and economic effects occurring at or near the farm level and those related to consumers, international trade, regulatory requirements, intellectual property, and food security. At the farm level, the available evidence indicates that soybean, cotton, and maize varieties with GE herbicide-resistant or insect-resistant traits (or both) have generally had favorable economic outcomes for producers who have adopted these crops, but there is high heterogeneity in outcomes. The utility of a GE variety depends on the fit of the GE trait and the genetics of the variety to the farm environment and the quality and cost of the GE seeds. In some situations in which farmers have adopted GE crops without identifiable economic benefits, the committee finds that increases in management flexibility and other considerations are driving adoption of GE crops, especially those with herbicide resistance.

Although GE crops have provided economic benefits to many small-scale farmers in the early years of adoption, enduring and widespread gains will depend on institutional support, such as access to credit, affordable inputs, extension services, and access to profitable local and global markets for the crops. Virus-resistant papaya is an example of a GE crop that is conducive to adoption by small-scale farmers because it addresses an agronomic problem but does not require concomitant purchase of such inputs as fertilizer or insecticides. GE plants with insect, virus, and fungus resistance and with drought tolerance were in development and could be useful to small-scale farmers if they are deployed in appropriate crops and varieties.

Evidence shows that GE crops with insect resistance and herbicide resistance differentially affect men and women, depending on the gendered division of labor for a specific crop and for particular localities. There is a small body of work demonstrating women's involvement in decision-making about planting new crop varieties and soil conservation has increased in farming households in general, including in households that have adopted GE crops. However, the analysis of the gender implications of GE crops remains inadequate. Subjects that need more study include differential access to information and resources and differential effects on time and labor use within farm households.

For the United States and Brazil, it is clear that where GE varieties have been widely adopted by farmers, the supply of non-GE varieties has declined, although they have not disappeared. There is uncertainty about the rate of progression of that trend in the United States, Brazil, and other countries. More research is needed to monitor and understand changes in variety diversity and availability.

For resource-poor smallholders who want to grow GE crops, the cost of GE seed may limit adoption. In most situations, differential cost of GE and non-GE seed is a small fraction of total costs of production, although it may constitute a financial constraint because of limited access to credit. In

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addition, small-scale farmers may face a financial risk when purchasing a GE seed upfront because the crop might fail; this may be an important consideration for small-scale farmers.

In the case of GE crops, adventitious presence is the unintended and accidental presence of low levels of GE traits in seeds, grains, or foods. Preventing adventitious presence is valuable for societal reasons because farmers want the freedom to decide what crops to grow on the basis of their skills, resources, and market opportunities and for economic reasons because markets are differentiated and organic and nonorganic, non-GE crops command a price premium. Questions about who is economically responsible for adventitious presence between farms remain unresolved in the United States. Strict private standards create an additional layer of complexity because producers may meet government guidelines for adventitious presence but fail to meet contract requirements set by private entities.

National governments make regulatory decisions about GE crops. That is appropriate, but as a consequence a GE crop may be approved for production in one country but not yet for importation into another. Alternatively, a GE crop-trait developer may not seek regulatory approval in importing jurisdictions, and this would raise the possibility that a product approved in one country may inadvertently reach a different country where it has not been approved. Those two situations are known collectively as asynchronous approval. Trade disruptions related to asynchronous approvals of GE crops and violations of an importing country's tolerance threshold have occurred and are likely to continue and to be expensive for exporting and importing countries.

The main purpose of any regulatory-approval system is to benefit society by preventing harm to public health and the environment and preventing economic harm caused by unsafe or ineffective products. There is a need to acknowledge that regulations also address more than those concerns and include a broad array of social, cultural, economic, and political factors that influence the distribution of risks and benefits, such as the intellectual-property and legal frameworks that assign liability. Regulations of GE crops inherently involve tradeoffs. They are necessary for biosafety and consumer confidence in the food supply, but they also have economic and social costs that can potentially slow innovation and deployment of beneficial products. The available evidence examined by the committee showcases the need to use a robust, consistent, and rigorous methodology to estimate the costs of regulations and the effects of regulation on innovation.

With regard to intellectual property, there is disagreement in the literature as to whether patents facilitate or hinder university-industry knowledge sharing, innovation, and the commercialization of useful goods. Whether a patent is applied to a non-GE or a GE crop, institutions with substantial legal and financial resources are capable of securing patent protections that limit access by small farmers, marketers, and plant breeders who lack resources to pay licensing fees or to mount legal challenges.

The committee heard diverse opinions on the ability of GE crops to affect food security in the future. GE crops that have already been commercialized have the potential to protect yields in places where they have been introduced, but they do not have greater potential yield than non-GE counterparts. GE crops, like other technological advances in agriculture, are not able by themselves to address fully the wide variety of complex challenges that face smallholders. Such issues as soil fertility, integrated pest management, market development, storage, and extension services will all need to be addressed to improve crop productivity, decrease post-harvest losses, and increase food security. More important, it is critical to understand that even if a GE crop may improve productivity or nutritional quality, its ability to benefit intended stakeholders will depend on the social and economic contexts in which the technology is developed and diffused.

Recommendations on Social and Economic Effects:

- Investments in GE crop research and development may be one of a number of potential approaches for solving agricultural production and food security problems because yield can be enhanced and stabilized by improving germplasm, environmental conditions, management practices, and socioeconomic and physical infrastructure. Policy-makers should determine the most cost-effective ways to distribute resources among those categories to improve production.

- More research to ascertain how farmer knowledge can help to improve existing regulations should be conducted. Research is also needed to determine whether genetic engineering in general or specific GE traits contribute to farmer deskilling and, if so, to what degree.
- A robust, consistent, and rigorous methodology should be developed to estimate the costs associated with taking a GE crop through the regulatory process.
- More research should be done to document benefits of and challenges to existing intellectual-property protection for GE and conventionally bred crops.
- More research should be conducted to determine whether seed market concentration is affecting GE seed prices and, if so, whether the effects are beneficial or detrimental for farmers.
- Research should be done on whether trait stacking (that is, including more than one GE trait in a variety) is leading to the sale of more expensive seeds than farmers need.
- Investment in basic research and investment in crops that do not offer strong market returns for private firms should be increased. However, there is evidence that the portfolio of public institutions has shifted to mirror that of private firms more closely.

PROSPECTS FOR GENETIC ENGINEERING

Plant-breeding approaches in the 21st century will be enhanced by increased knowledge of the genetic basis of agronomic traits and by advances in the tools available for deciphering the genomes and metabolic makeup of thousands of plants. That is true for conventional breeding and for breeding that includes genetic engineering. The rapid progress of genome-editing tools, such as CRISPR/Cas9, should be able to complement and extend contemporary methods of genetic improvement by increasing the precision with which GE changes are made in the plant genome.

Emerging -omics technologies are being used to assess differences between GE plants and their non-GE counterparts in their genomes, the genes expressed in their cells, and the proteins and other molecules produced by their cells. Some of the technologies require further refinement before they can be of value to regulatory agencies for assessing health and environmental effects.

The new molecular tools being developed are further blurring the distinction between genetic changes made with conventional breeding and with genetic engineering. For example, CRISPR/Cas9 could be used to make a directed change in the DNA of a crop plant that would alter a couple of amino acids of a protein and lead to increased resistance to a herbicide. Alternatively, the new tools for deciphering the DNA sequences of full genomes can be used after genome-wide chemical-induced or radiation-induced mutagenesis in thousands of individual plants to isolate the one or few plants that have only the mutations resulting in the amino acids that confer resistance to the same herbicide. Both traits are developed with new molecular tools and would appear to have similar risks and benefits, but the plants derived from one approach are currently classified as genetically engineered and those derived from the other are considered conventionally bred.

In many cases, both genetic engineering and modern conventional breeding could be used to enhance a crop trait, such as insect resistance or drought tolerance. However, in some cases, a new trait can be conferred on a crop only through genetic engineering because the required genetic variation cannot be accessed through sexual crosses. In other cases, at least in the foreseeable future, when dozens or hundreds of genes contribute to an enhanced trait, conventional breeding is the only viable approach for achieving the desired outcome. More progress in crop improvement could be made by using conventional breeding and genetic engineering jointly rather than in isolation.

The emerging technologies are expected to result in increased precision, complexity, and diversity in GE crop development. Because they have been applied to plants only recently, it is difficult to predict the scope of their potential uses for crop improvement in the coming decades. However, traits that were being explored when the committee was writing its report included improved tolerance to abiotic

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stresses, such as drought and thermal extremes; increased efficiency in plant biological processes, such as photosynthesis and nitrogen use; and improved nutrient content. Expansion of traits that respond to biotic stresses—such as fungal and bacterial diseases, insects, and viruses—is likely.

One of the critical questions about the new traits that may be produced with emerging genetic-engineering technologies is the extent to which these traits will contribute to feeding the world in the future. Some crop traits, such as insect and disease resistance, are likely to be introduced into more crop species and the number of pests targeted will also likely increase. If deployed appropriately, those traits will almost certainly increase harvestable yields and decrease the probability of losing crop plantings to major insect or disease outbreaks. However, there is great uncertainty regarding whether traits developed with emerging genetic-engineering technologies will increase crop potential yield by improving photosynthesis and increasing nutrient use. Including such GE traits in policy planning as major contributors to feeding the world must be accompanied by strong caveats.

Another major question posed by researchers and members of the public is whether GE crops will increase yields per hectare without adverse environmental effects. Experience with GE insect-resistant crops leads to an expectation that such traits will not have adverse environmental effects as long as the traits affect only a narrow spectrum of insects. For other traits, such as drought tolerance, appropriate use could be ecologically benign, but if short-term profit goals lead to the expansion of crops into previously unmanaged habitats or to the unsustainable use of agricultural lands, that could result in decreased global biodiversity and undesirable variation in crop yields. Certainly, deployment of new crops in ways that increase the long-term economic sustainability of resource-poor farmers could result in improvement in environmental sustainability.

Recommendations on Prospects for Genetic Engineering:

- To realize the potential of -omics technologies to assess intended and unintended effects of new crop varieties on human health and the environment and to improve the production and quality of crop plants, a more comprehensive knowledge base of plant biology at the systems level (DNA, RNA, protein, and metabolites) should be constructed for the range of variation inherent in both conventionally bred and genetically engineered crop species.
- Balanced public investment in these emerging genetic-engineering technologies and in a variety of other approaches should be made because it will be critical for decreasing the risk of global and local food shortages.

REGULATION OF CURRENT AND FUTURE GENETICALLY ENGINEERED CROPS

Risk analyses and assessments of GE crops offer technical support for regulatory decision-making but also establish and maintain the legitimacy of government regulatory authorities. The committee examined the systems used by the United States, the European Union, Canada, and Brazil to regulate GE plants. All the systems have evolved over time and have unique characteristics. The European Union and Brazil have chosen to regulate genetic engineering specifically, excluding conventional and other breeding methods. Canada has chosen to regulate foods and plants on the basis of novelty and potential for harm, regardless of the breeding technique used. The United States has relied on existing laws to regulate GE crops. In theory, the U.S. policy is a "product"-based policy, but USDA and EPA determine which plants to regulate at least partially on the basis of how they were developed. All four regulatory systems use guidelines set out by the Codex Alimentarius Commission and other international bodies, and all start with comparison of the GE or novel crop variety with a known, conventionally bred counterpart. They differ in stringency of testing, in what they consider to be relevant differences, in the types of agencies that conduct the risk analysis and risk assessment, and in how the public is involved.

It is not surprising to find a diversity of regulatory processes for products of genetic engineering because they mirror the broader social, political, legal and cultural differences among countries. Not all issues can be answered by technical assessments alone. Indeed, conclusions about GE crops often depend on how stakeholders and decision-makers set priorities for and weigh different considerations and values. Disagreements among countries about regulatory models and resulting trade disagreements are expected to continue to be part of the international landscape.

Emerging genetic-engineering technologies challenge most existing regulatory systems by blurring the distinction between genetic engineering and conventional plant breeding while enabling increasingly profound alterations of plant metabolism, composition, and ecology. As pointed out in previous National Research Council reports, it is the product, not the process, that should be regulated. It must be emphasized that the size and extent of a genetic change itself, whether the change is produced by genetic engineering or by conventional breeding, have relatively little relevance to the extent of change in a plant and consequently to the risk that it poses to the environment or food safety. It is the change in the actual characteristics of the plant, intended and unintended, that should be assessed for risks. Recent developments in -omics technologies have made thorough assessments of those characteristics of plants attainable in the near future. Even in their current state of development, the technologies could enable a tiered approach to regulatory testing in which any new variety shown to have no new intended traits with health or environmental concerns and no unintended alterations of concern in its composition would be exempted from further testing (Figure S-3). The costs of -omics methods are decreasing, but even current costs are low relative to the cost of other components of regulatory assessments.

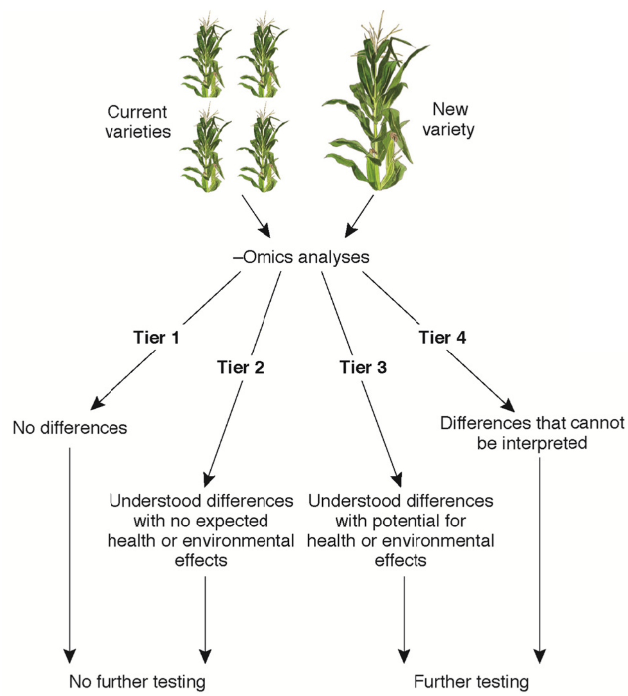

FIGURE S-3 Proposed tiered crop evaluation strategy crops using -omics technologies.[8] NOTE: A tiered set of paths can be taken, depending on the outcome of the various -omics technologies. In Tier 1, there are no differences between the variety under consideration and a set of conventionally bred varieties that represent the range of genetic and phenotypic diversity in the species. In Tier 2, differences that are well understood to have no expected adverse health effects are detected. In Tiers 3 and 4, differences that may have potential health or environmental effects are detected and thus require further safety testing.

[8]Illustration by R. Amasino.

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Recommendations on Regulations:

- In addition to issues of product safety, socioeconomic issues that go beyond product safety are technology-governance issues that should be addressed by policy-makers, the private sector, and the public in a way that considers competing interests of various stakeholders and inherent tradeoffs.
- Regulating authorities should be particularly proactive in communicating information to the public about how emerging genetic-engineering technologies (including genome editing and synthetic biology) or their products might be regulated and about how new regulatory methodologies (such as the use of -omics technologies) might be used. They should also be proactive in seeking input from the public on these issues.
- In deciding what information to exclude from public disclosure as confidential business information or on other legal grounds, regulating authorities should bear in mind the importance of transparency, access to information, and public participation and should ensure that exemptions are as narrow as possible.
- Regulatory agencies responsible for environmental risk should have the authority to impose continuing requirements and require environmental monitoring for unexpected effects after a GE crop has been approved for commercial release.
- In determining whether a new plant variety should be subject to premarket government approval for safety, regulators should focus on the extent to which the novel characteristics of the plant variety (both intended and unintended) are likely to pose a risk to human health or the environment, the extent of uncertainty regarding the severity of potential harm, and the potential for exposure, regardless of the process by which the novel plant variety was bred.

The committee offers that final recommendation because the process-based approach has become less and less technically defensible as the old approaches to genetic engineering become less novel and the emerging processes fail to fit old categories of genetic engineering. Moreover, because the emerging technologies have the potential to make both incremental changes that lack substantial risk and major changes that could be problematic, the committee recommends that a tiered approach to regulation should be developed that uses trait novelty, potential hazard, and exposure as criteria. -Omics technologies will be critical for such an approach. The committee is aware that those technologies are new and that not all developers of new varieties will have access to them; therefore, public investment will be needed.