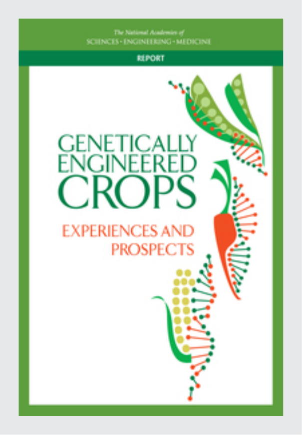

Genetically Engineered Crops: Experiences and Prospects

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GENETICALLY ENGINEERED CROPS

EXPERIENCES AND PROSPECTS

Committee on Genetically Engineered Crops:
Past Experience and Future Prospects

Board on Agriculture and Natural Resources

Division on Earth and Life Studies

The National Academies of
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Preface

Our committee was given the task of examining the evidence regarding potential negative effects and benefits of currently commercialized genetically engineered (GE) crops and the potential benefits and negative effects of future GE crops. In carrying out this study, the committee members and I were well aware of the controversial nature of genetic engineering in the United States and globally. Before and during the committee's first meeting, we received comments from people and groups expressing the view that the scientific evidence establishing the safety of current GE crops was so solid and well-reviewed that the only potentially useful task for the committee would be to examine emerging genetic-engineering technologies. We considered those comments but believed that available analyses were not complete and up to date and that an examination of the data on diverse biological and societal aspects of both current and future GE crops would therefore be useful. We received other comments indicating that research studies that found adverse biological or social effects of GE crops had been ignored, and because of our committee's composition, we too would probably ignore them. We took all of the comments as constructive challenges.

Our committee embraced the National Academies consensus-study process, which requires that "efforts are made to solicit input from individuals who have been directly involved in, or who have special knowledge of, the problem under consideration" and that a study "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." We listened to presentations from 80 people who had diverse expertise, experience, and perspectives on GE crops to augment the diversity represented on the committee; they are listed in Appendixes C and D. We also received and read more than 700 comments and documents sent to us from individuals and organizations about specific risks and benefits that could be associated with GE crops and their accompanying technologies. Beyond those sources of information, our committee carefully examined literature—peer-reviewed and nonreviewed—relevant to benefits and risks associated with GE crops in the United States and elsewhere.

Although it is true that articles exist that summarize much of the literature on GE crops, we committed ourselves to taking a fresh look at the primary literature itself. Our major goal in writing this report was to make available to the public, to researchers, and to policy-makers a comprehensive review of the evidence that has been used in the debates about GE crops and information on relevant studies that are rarely referred to in the debates. Given the immense literature on GE crops, we suspect that we missed some relevant articles and specific results.

We received a number of broad comments that asked us to examine and make judgments about the merits of technology-intensive agriculture compared with more agroecological approaches. That would be an important comparison but was beyond the scope of the specific task given to the committee.

We recognized that some members of the public are skeptical of the literature on GE crops because of concerns that many experiments and results have been conducted or influenced by the industries that are profiting from these crops. Therefore, when we referred to articles in the three major chapters (4, 5, and 6) of the report regarding current GE crops, we identified the affiliations of their primary authors and, when possible, the specific sources of their funding. That information is available on our study's website (http://nas-sites.org/ge-crops/).

To make the basis of each of our report's conclusions accessible, we developed a user-friendly interface on the website that can be queried for each specific finding and recommendation in the report. The interface takes a user to the text in the report that culminated in each finding or recommendation. A second interface on the website has a summary list of the comments and questions that were sent to us by the public or brought up in formal presentations; this interface enables a user to read how the committee addressed a specific comment or question.

We worked hard to analyze the existing evidence on GE crops, and we made recommendations based on our findings; ultimately, however, decisions about how to govern new crops need to be made by societies. There is an indisputable case for regulations to be informed by accurate scientific information, but history makes clear that solely "science-based regulation" is rare and not necessarily desirable. As a small example, how would science alone decide on how important it is to prevent a decline in monarch butterfly populations?

We received impassioned requests to give the public a simple, general, authoritative answer about GE crops. Given the complexity of the issues, we did not see that as appropriate. However, we hope that we have given the public and policy-makers abundant evidence and a framework to inform their decisions about individual agricultural products.

In 1999, Secretary of Agriculture Dan Glickman gave a speech[1] about biotechnology in which he stated that "with all that biotechnology has to offer, it is nothing if it's not accepted. This boils down to a matter of trust. Trust in the science behind the process, but particularly trust in the regulatory process that ensures thorough review—including complete and open public involvement." Trust must be based on more than authority and appealing arguments for or against genetic engineering. In this regard, while we recognize that no individual report can be completely balanced, we offer our report as a sincere effort at thoroughness and openness in examining the evidence related to prevalent claims about GE crops.

ACKNOWLEDGMENTS

First and foremost, our committee is grateful to Kara Laney, our study director. Without her perseverance, dedication to excellence, amazing grasp of the literature, writing skills, and talent for coaxing the best possible efforts from committee members, this report would have been a shadow of itself. Jenna Briscoe provided incredible behind-the-scenes support for everything that the committee did. Janet Mulligan, our senior program associate for research, enabled access to nearly inaccessible documents and kept incoming public comments and articles organized. Maria Oria, a senior program officer with the National Academies Food and Nutrition Board, provided expert assistance with food-safety sections of the report. Norman Grossblatt substantially improved the language in our report. We thank Robin Schoen, director of the Board on Agriculture and Natural Resources, for encouraging the committee to abandon preconceived notions, listen to diverse voices, and dig deeply into the evidence regarding risks and benefits associated with GE crops. The committee's thinking was challenged, broadened, and deepened by the many people who participated in committee meetings and webinars and the organizations and individuals that

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[1] Glickman, D. 1999. Speech to the National Press Club, Washington, DC, July 13. Reprinted on pp. 45–58 in Environmental Politics Casebook: Genetically Modified Foods, N. Miller, ed. Boca Raton, FL: Lewis Publishers.

submitted comments to us. We are thankful for their insights. Finally, we thank all the external reviewers of the report for helping us to improve its accuracy.

Fred Gould, *Chair*
Committee on Genetically Engineered Crops:
Past Experience and Future Prospects

Acknowledgment of Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

Katie Allen, Murdoch Childrens Research Institute
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Steve Bradbury, Iowa State University
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the report's conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Lynn Goldman**, George Washington University, and **Allison A. Snow**, Ohio State University. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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APPENDIXES

Executive Summary

Since the 1980s, biologists have used genetic engineering of crop plants to express novel traits. For various reasons, only two traits—insect resistance and herbicide resistance—had been genetically engineered into a few crop species and were in widespread use in 2015. Many claims of positive and negative effects of existing genetically engineered (GE) crops have been made. A main task of the Committee on Genetically Engineered Crops: Past Experience and Future Prospects was to examine the evidence related to those claims. The committee was also asked to assess emerging genetic-engineering technologies, how they might contribute to crop improvement, and what technical and regulatory challenges they may present. The committee delved into the relevant literature, heard from 80 diverse speakers, and read more than 700 comments from members of the public to broaden its understanding of issues surrounding GE crops. It concluded that sweeping statements about GE crops are problematic because issues related to them are multidimensional.

The available evidence indicates that GE soybean, cotton, and maize have generally had favorable economic outcomes for producers who have adopted these crops, but outcomes have been heterogeneous depending on pest abundance, farming practices, and agricultural infrastructure. The crops with the insect-resistant trait—based on genes from a bacterium (*Bacillus thuringiensis*, or *Bt*)—generally decreased yield losses and the use of insecticides on small and large farms in comparison with non-*Bt* varieties. In some cases, widespread planting of those crops decreased the abundance of specific pests in the landscape and thereby contributed to reduced damage even to crops that did not have the *Bt* trait, and planting *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. However, in locations where resistance-management strategies were not followed, damaging levels of resistance evolved in some target insects. Herbicide-resistant (HR) crops sprayed with the herbicide glyphosate often had small increases in yield in comparison with non-HR counterparts. Farm-level surveys did not find lower plant diversity in fields with HR crops than in those planted with non-GE counterparts. In areas where planting of HR crops led to heavy reliance on glyphosate, some weeds evolved resistance and present a major agronomic problem. Sustainable use of *Bt* and HR crops will require use of integrated pest-management strategies.

There have been claims that GE crops have had adverse effects on human health. Many reviews have indicated that foods from GE crops are as safe as foods from non-GE crops, but the committee re-examined the original studies of this subject. The design and analysis of many animal-feeding studies were not optimal, but the large number of experimental studies provided reasonable evidence that animals were not harmed by eating food derived from GE crops. Additionally, long-term data on livestock health before and after the introduction of GE crops showed no adverse effects associated with GE crops. The committee also examined epidemiological data on incidence of cancers and other human-health problems over time and found no substantiated evidence that foods from GE crops were less safe than foods from non-GE crops.

The social and economic effects of GE crops depend on the fit of the GE trait and the plant variety to the farm environment and the quality and cost of the GE seeds. GE crops have benefited many farmers on all scales, but genetic engineering alone cannot address the wide variety of complex challenges that face farmers, especially smallholders. Given the complexities of agriculture and the need for cohesive planning and execution, public and private support is essential if societal benefits are to be maximized over a long period and in different areas.

Molecular biology has advanced substantially since the introduction of GE crops two decades ago. Emerging technologies enable more precise and diverse changes in crop plants. Resistance traits aimed at a broader array of insect pests and diseases in more crops are likely. Research to increase potential yields and nutrient-use efficiencies is under way, but it is too early to predict its success. The committee recommends a strategic public investment in emerging genetic-engineering technologies and other approaches to address food security and other challenges.

-Omics technologies enable an examination of a plant's DNA sequence, gene expression, and molecular composition. They require further refinements but are expected to improve efficiency of non-GE and GE crop development and could be used to analyze new crop varieties to test for unintended changes caused by genetic engineering or conventional breeding.

National regulatory processes for GE crops vary greatly because they mirror the broader social, political, legal, and cultural differences among countries. Those differences are likely to continue and to cause trade problems. Emerging technologies have blurred the distinction between genetic engineering and conventional plant breeding to the point where regulatory systems based on process are technically difficult to defend. The committee recommends that new varieties—whether genetically engineered or conventionally bred—be subjected to safety testing if they have novel intended or unintended characteristics with potential hazards. It proposes a tiered approach to regulation that is based in part on new -omics technologies that will be able to compare the molecular profiles of a new variety and a counterpart already in widespread use. In addition, GE crop governance should be transparent and participatory.

Summary

Genetic engineering—a process by which humans introduce or change DNA, RNA, or proteins in an organism to express a new 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).[1] A few other GE

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

FIGURE S-1 Type and location of commercially grown genetically engineered (GE) crops in 2015.
SOURCE: 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.
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.

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 National 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.

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 prac-

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 genetic-engineering technology.

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

tice, 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 trait–crop 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 National Academies study process requires that, in all 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 National Research Council report and the National 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

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

[3] For more information about the National 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.

[5] These presentations were recorded and can be viewed at http://nas-sites.org/ge-crops/.

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.

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

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[6] Isolines = individuals that differ genetically from one another by only a small number of genetic loci.

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.

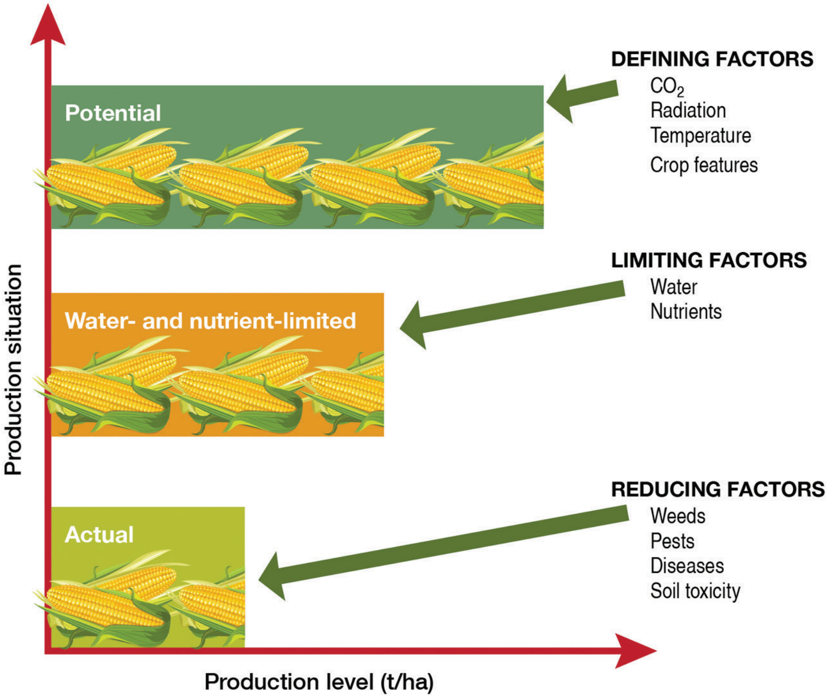

FIGURE S-2 Factors that determine crop yield.
SOURCE: Based on van Ittersum, M.K., K.G. Cassman, P. Grassini, J. Wolf, P. Tittonell, and Z. Hochman. 2013. Yield gap analysis with local to global relevance—a review. Field Crops Research 143:4–17.
NOTE: Potential yield is the theoretical yield that a crop genotype can achieve without any limitations of water or nutrients and without losses to insect pests, weeds, 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.

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.

Herbicide-resistant 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 conventionally bred 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-resistant 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. There-

fore, 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 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 crop 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 issued a monograph in which it classified glyphosate in 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 on 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 found 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 pesticides. 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 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 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.

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, regu-

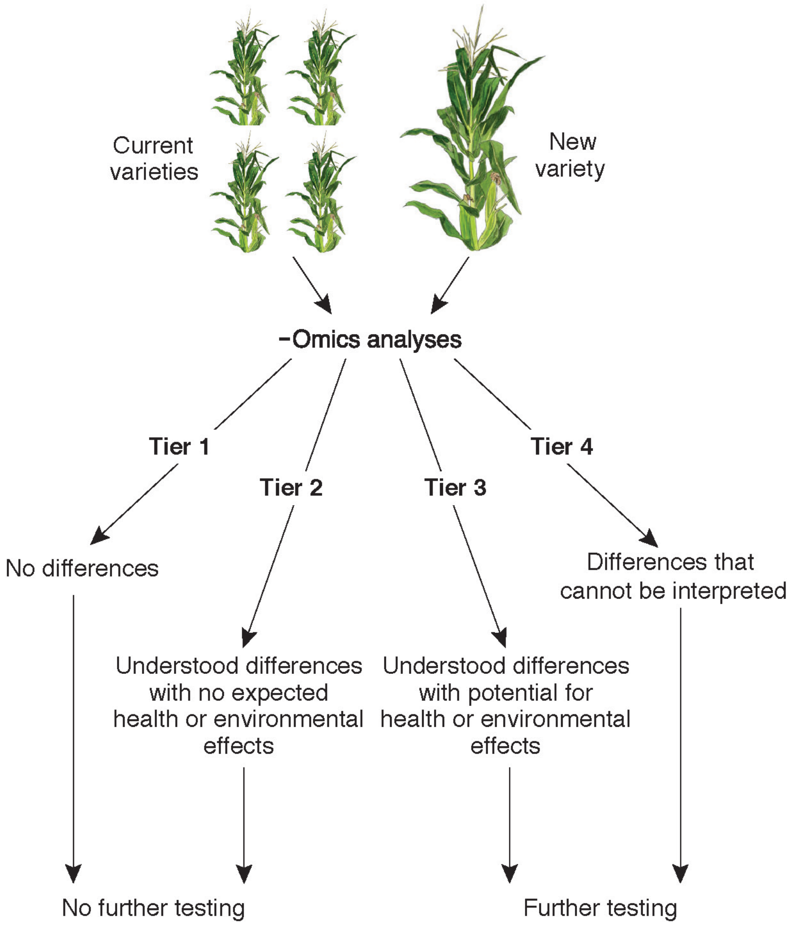

FIGURE S-3 Proposed tiered crop evaluation strategy crops using -omics technologies.
SOURCE: Illustration by R. Amasino.
NOTE: A tiered set of paths can be taken, depending on the outcome of the various -omics technologies. In Tier 1, there are no differences between the variety under consideration and 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.

lating 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.

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The Study of Genetically Engineered Crops by the National Academies of Sciences, Engineering, and Medicine

The National Academies of Sciences, Engineering, and Medicine have been involved in assessing and recommending science policy related to genetic engineering since the advent of the technology in the 1970s. Over the years, the National Academies have often been called on to address questions specifically about the use of the technology in connection with agricultural crops. In 2014, the National Academies formed the Committee on Genetically Engineered Crops: Past Experience and Future Prospects to undertake a broad retrospective examination of the technology and to anticipate what evolving scientific techniques in genetic engineering hold for the future of agriculture. The committee's present report builds on and updates concepts and questions raised in previous National Academies reports.

THE NATIONAL ACADEMIES AND GENETIC ENGINEERING IN AGRICULTURE

President Abraham Lincoln established the National Academy of Sciences (NAS) under a congressional charter in 1863. As nongovernmental organizations, it and its fellow academies, the National Academy of Engineering and the National Academy of Medicine,[1] provide independent scientific advice to the U.S. federal government. Known together as the National Academies of Sciences, Engineering, and Medicine, they convene ad hoc committees to write expert reports on matters involving science, engineering, technology, and health. The independent reports are often

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[1] Until 2015, the National Academy of Medicine was known as the Institute of Medicine.

produced at the request of U.S. federal agencies or other sponsoring organizations. Until 2015, National Academies reports were published under the authorship of the National Research Council.

The National Academies first convened such a committee on the topic of genetic engineering in 1974. Recombinant-DNA technology made possible the introduction of genetic material from an organism into an unrelated organism, and it held great potential for furthering the study of genetics. However, there was concern that introducing genetic material, for example, from bacteria into an animal virus, could have unforeseen and perhaps deleterious consequences for human and animal health and for the environment. Therefore, scientists attending the Gordon Research Conference on Nucleic Acids in 1973 urged the president of NAS to form the Committee on Recombinant DNA Molecules to "consider this problem and to recommend specific actions or guidelines" (Singer and Soll, 1973).

In its 1974 report, the Committee on Recombinant DNA Molecules recognized that there was "serious concern that some of these artificial recombinant-DNA molecules could prove biologically hazardous" (Berg et al., 1974).[2] The committee suggested that NAS convene an international meeting to "review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules" (Berg et al., 1974).

In the subsequent decade, NAS organized three large meetings on genetic engineering. The first was the 1975 International Conference on Recombinant DNA Molecules at the Asilomar Conference Center in California, the direct result of the recommendation by the Committee on Recombinant DNA Molecules. Participants assessed the potential risks posed by different types of recombinant-DNA experiments. The conference informed an advisory committee of the U.S. National Institutes of Health that was tasked with issuing guidelines on recombinant-DNA research. The second was a 1977 forum on research with recombinant DNA, "initiated by the National Academy of Sciences to make a contribution to national policy in areas at the interface of science and society" (NAS, 1977:1). The forum not only discussed the current and future state of the technology but was a venue for airing and debating the moral and ethical implications of and disagreements about its use. The third was a convocation organized specifically around the topic of genetic engineering in agriculture. By the early 1980s, the technology had advanced from basic work in cells to more complex organisms, including plants. Plant scientists were using genetic engineering to gain a better understanding of plant biology and to identify

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[2] Chapter 3 of the present report provides more detail on the nature of the concerns and the recommendations provided by the Committee on Recombinant DNA Molecules. See the section "Policy Responses to Scientific and Public Concerns."

agriculturally important genes. The convocation of scientists and policymakers in the U.S. government, universities, and private companies in 1983 focused on agricultural research opportunities and policy concerns regarding genetic engineering in plants, which the participants anticipated would be ready for commercial application within the next 10 years (NRC, 1984).

As the plausibility of taking genetically engineered (GE) organisms (including plants) outside the laboratory increased, the NAS Council[3] convened a committee of biologists to write a white paper on the introduction of recombinant-DNA–engineered organisms into the environment. The council took this self-initiated step in response to the needs that it perceived to "distinguish between real and hypothetical problems" and to "assess in a rational manner concerns about possible adverse environmental effects" (NAS, 1987:5). The white paper, issued in 1987, concluded that "the risks associated with the introduction of R[ecombinant]-DNA–engineered organisms are the same as those associated with the introduction of unmodified organisms and organisms modified by other methods" (NAS, 1987:6) and that such organisms posed no unique environmental hazards.

Since the mid-1980s, the National Academies have provided expert advice as the science of genetic engineering in agriculture has advanced, starting before the commercialization of GE crops and continuing more than two decades after the first GE crop was sold. The advice has been issued in the form of National Research Council consensus reports developed by ad hoc committees with relevant expertise (Table 1-1). Many of these reports were sponsored by the U.S. government agencies charged with regulating GE crops: the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA), the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration.

Genetic-engineering techniques have advanced considerably since the first National Research Council report on this topic was published. As is evident from Table 1-1, the National Academies have often been called on to evaluate the potential effects on human and animal health and on the environment as genetic engineering has evolved. In addition to examining the natural science related to genetic engineering in agriculture, many National Research Council reports have pointed out the need for social-science research on societal effects and greater social engagement with the public on the topic of GE crops. For example, the authoring committee of *Agricultural Biotechnology: Strategies for National Competitiveness* urged the education of the public about biotechnology to "adequately inform regulators and the public about both the benefits and possible risks involved" in future applications of the technology (NRC, 1987:9). The authoring committee of *Environmental Effects*

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[3] The NAS Council consists of the NAS president and other NAS members elected by the Academy.

TABLE 1-1 National Research Council Consensus Reports on Genetic Engineering in Agriculture, 1985–2010[a]

Report Title	Publication Year	Sponsor	Task
New Directions for Biosciences Research in Agriculture: High-Reward Opportunities	1985	U.S. Department of Agriculture–Agricultural Research Service (USDA–ARS)	Identify how USDA–ARS could use molecular genetic techniques to yield new insights in basic studies of food animals, crop plants, plant pathogens, and insect pests
Agricultural Biotechnology: Strategies for National Competitiveness	1987	Foundation for Agronomic Research, Richard Lounsbery Foundation, USDA–ARS, National Research Council Fund	Develop strategies for national competitiveness in agricultural biotechnology and study public-sector and private-sector interactions in biotechnology research
Field Testing Genetically Modified Organisms: Framework for Decisions	1989	Biotechnology Science Coordinating Committee[b]	Evaluate scientific information pertinent to decision-making regarding the introduction of genetically modified plants and microorganisms into the environment[c]
Genetically Modified Pest-Protected Plants: Science and Regulation	2000	National Academy of Sciences (NAS)	Investigate the risks and benefits of genetically modified pest-protected plants and the framework used by the United States to regulate these plants and revisit the conclusions of the 1987 NAS Council white paper
Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation	2002	USDA	Examine the scientific basis supporting the scope and adequacy of USDA's regulatory oversight of environmental issues related to GE crops

Conclusions/Recommendations
Report identified areas in which new molecular genetic techniques could be most useful in basic studies of food animals, crop plants, plant pathogens, and insect pests and steps USDA–ARS could take to create an optimal climate for productive research.
Report recommended an increased emphasis on basic research, greater efforts to apply techniques of biotechnology to problems in agricultural sciences, and increased attention to developing a body of knowledge about the ecological aspects of biotechnology in agriculture. It outlined the roles federal and state governments and private sector could play in funding research and in product development.
Report stated that plants modified by conventional-breeding methods were safe and that crops modified by molecular and cellular methods should not pose different risks. The likelihood of enhanced weediness from genetically modified, highly domesticated crops was low.
Report found no evidence that foods derived from genetically engineered (GE) crops were unsafe to eat. It concluded that the U.S. regulatory framework was effective but made suggestions for improving it on the assumption that more types of GE crops would be introduced and called for research to determine whether long-term animal-feeding trials were needed for transgenic pest-protected plants. It found that the conclusions of the 1987 white paper were valid for the products commercially available at the time and observed that plants produced with new recombinant-DNA methods not involving plant-pest genes might not fall under the regulatory jurisdiction of USDA.
Report found that the transgenic process presented no new categories of risk compared to conventional methods of crop improvement. It concluded that USDA had improved and continued to improve its regulatory system as it learned from new challenges. It recommended the process be made more transparent and rigorous and include post-commercialization monitoring and suggested that USDA include in its deregulation assessments potential effects of GE crops on regional farming practices or systems. Report was the first to examine how commercial use of GE crops with nonpesticidal traits could affect agricultural and nonagricultural environments and the first to provide guidance for assessing the potential cumulative environmental effects of commercialized GE crops on large spatial scales over many years.

continued

TABLE 1-1 Continued

Report Title	Publication Year	Sponsor	Task
Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects	2004	USDA, U.S. Food and Drug Administration (FDA), and U.S. Environmental Protection Agency (EPA)	Outline science-based approaches for assessing or predicting the unintended health effects of GE foods and compare the potential for unintended effects with those of foods derived from other conventional genetic modification methods
Biological Confinement of Genetically Engineered Organisms	2004	USDA	Evaluate three general strategies for those GE organisms that require biological confinement: reducing the spread or persistence of GE organisms, reducing unintended gene flow from GE organisms to other organisms, and limiting expression of transgenes
The Impact of Genetically Engineered Crops on Farm Sustainability in the United States	2010	National Academies	Review and analyze published literature on impact of GE crops on the productivity and economics of farms in the United States; examine evidence for changes in agronomic practices and inputs; evaluate producer decision-making with regard to the adoption of GE crops

[a] In addition to consensus reports, the National Academies have held a number of workshops, symposia, and forums on various aspects of genetic engineering in agriculture. See *Biotechnology and the Food Supply: Proceedings of a Symposium* (1988); *Plant Biotechnology Research for Developing Countries* (1990); *Intellectual Property Rights and Plant Biotechnology* (1997); *Designing an Agricultural Genome Program* (1998); *Ecological Monitoring of Genetically Modified Crops: A Workshop Summary* (2001); *Genetically Engineered Organisms, Wildlife, and Habitat: A Workshop Summary* (2008); and *Global Challenges and Directions for Agricultural Biotechnology: Workshop Report* (2008). All consensus reports and other National Academies products are available at www.nap.edu.

[b] Members of the Biotechnology Science Coordinating Committee were drawn from USDA, EPA, FDA, the National Institutes of Health, and the National Science Foundation.

[c] The statement of task for *Field Testing Genetically Modified Organisms: Framework for Decisions* pertained to ecological risks posed by small-scale field tests. It did not include potential human health risks or issues that could arise from large-scale commercial planting of GE crops.

Conclusions/Recommendations
Report concluded that all available evidence indicated that unexpected or unintended changes may occur with all forms of genetic modification—including genetic engineering—and that compositional changes from any kind of genetic change, whether through genetic engineering or by other means, did not automatically lead to unintended adverse health effects. Report noted that no adverse health effects attributed to genetic engineering had been documented in the human population.
Report found insufficient data or inadequate scientific techniques to assess effective biological confinement methods. When biological confinement was needed, it would require safe practices by designers and developers of GE organisms, effective regulatory oversight, and transparency and public participation when appropriate techniques and approaches were being developed and implemented.
Found genetic-engineering technology had produced substantial net environmental and economic benefits to U.S. farmers compared with non-GE crops in conventional agriculture but that those benefits had not been universal and could change over time and that the social effects of the technology were largely unexplored. Going forward, the potential risks and benefits associated with GE crops were likely to be more numerous because the technology would probably be applied to a greater variety of crops in the future.

of Transgenic Plants: The Scope and Adequacy of Regulation recommended that APHIS work to involve interested groups and affected parties more in its risk-analysis process while maintaining a scientific basis for decisions because "public confidence in biotechnology will require that socioeconomic impacts are evaluated along with environmental risks and that people representing diverse values have an opportunity to participate in judgments about the impacts of the technology" (NRC, 2002:15). The Committee on Genetically Engineered Crops: Past Experience and Future Prospects—which was tasked with examining both the benefits and the direct or indirect adverse effects on human and animal health, the environment, and society—followed this advice by taking many steps to involve interested groups during the process of writing its report while it consulted, reviewed, and built on the findings and recommendations of many preceding National Research Council reports (see section below "Soliciting Broad Input from Different Perspectives and Evaluating Information").

THE COMMITTEE AND ITS CHARGE

In 2014, committee members for the study "Genetically Engineered Crops: Past Experience and Future Prospects" were approved by the NAS president from among several hundred persons nominated during the committee-formation phase of the study. Committee members are chosen for their individual expertise, not their affiliation to any institution, and they volunteer their time to serve on a study. The present committee was comprised of experts with backgrounds in diverse disciplines.[4] Fields of

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[4] Every National Academies committee is provisional until the appointed members have had an opportunity to discuss as a group their points of view and any potential conflicts of interest related to the statement of task. They also determine whether the committee is missing expertise that may be necessary to answer questions in the statement of task. As part of their discussion, committee members consider comments submitted by the public about the committee's composition. The discussion takes place in the first in-person meeting of the committee. The committee is no longer provisional when it has determined that no one with an avoidable conflict of interest is serving on the committee and that its membership has the necessary expertise to address the statement of task.

The Committee on Genetically Engineered Crops: Past Experience and Future Prospects did not identify any conflicts of interest among its members. However, in light of comments received from the public before its first meeting and because of two resignations around the time of the first meeting, one new member with experience in molecular biology and two new members with international experience and expertise in sociology were added to the committee. Those appointments brought the committee's membership to 20. That is a large committee for the National Academies, but it ensured that diverse perspectives were represented in committee discussions and in the final report.

For more information about the National Academies study process, including definitions and procedures related to points of view and conflicts of interest, visit http://www.nationalacademies.org/studyprocess/. Accessed July 14, 2015.

expertise represented on the committee included plant breeding, agronomy, ecology, food science, sociology, toxicology, biochemistry, life-sciences communication, molecular biology, economics, law, weed science, and entomology. Biographies of the committee members are in Appendix A.

A statement of task guides each National Academies study and determines what kinds of expertise are needed on a committee. A committee writes a report to answer as rigorously as possible the questions posed in the statement of task. The committee members for the present study were therefore selected because of the relevance of their experience and knowledge to the study's specific statement of task (Box 1-1).

The sponsors of the study were the Burroughs Wellcome Fund, the Gordon and Betty Moore Foundation, the New Venture Fund, and USDA. The study also received funding from the National Academy of Sciences itself. Sponsors and the National Academies often negotiate the questions contained in a study's statement of task, including the task for this study, before a study begins. Sponsors may also nominate persons to serve on a committee, but they do not have a role in selecting who is appointed and do not have access to the committee during its deliberations or to its report before the report is approved for public release.

SOLICITING BROAD INPUT FROM DIFFERENT PERSPECTIVES AND EVALUATING INFORMATION

The National Academies study process states that in all National 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"[5] 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."[6] The committee began to address the issues in the statement of task in the information-gathering phase of its study, during which it made a concerted effort to hear from many presenters on a variety of topics and to listen to a broad array of positions regarding GE crops.

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

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

BOX 1-1
Statement of Task[a]

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 genetic-engineering technology.

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

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[a] The committee reviewed the statement of task during its first meeting. It then adjusted the language in the statement of task to ensure that its goals were clearly presented. Appendix B shows the changes in the statement of task.

Information-Gathering Meetings and Webinars

Committees convened by the National Academies invite speakers to make presentations during the course of their studies. Speakers are invited to provide a committee with information about specific topics relevant to a study's statement of task. Whenever a National Academies committee holds a meeting with invited presenters, the meeting is open to the public.

The committee held three public meetings and 15 webinars on a variety of topics (Table 1-2) in the period September 2014–May 2015. In all, the committee heard 80 invited presentations. Many committee members also attended a 1-day workshop that compared the environmental effects of pest-management practices among cropping systems, which featured 12 additional speakers.[7] The number of presentations made to the committee greatly exceeds that of previous National Academies committees that were convened to examine GE crops.[8] Over the course of the study, the committee heard from speakers not only from the United States but also France, the United Kingdom, Germany, Canada, and Australia as well as representatives from the African Union, the World Trade Organization, and the European Food Safety Authority.[9]

Members of the public were also encouraged to attend the meetings, and the committee made a concerted effort to use technologies that enabled people to view the meetings if they could not be present. All in-person, public meetings were webcast live, members of the public could listen to webinars, and recordings of the presentations at the meetings and webinars were archived on the study's website. The workshop on comparative pest management was also open to the public, webcast live, and recorded and archived.[10] Over the course of the information-gathering phase of the study, more than 500 people attended or remotely joined at least one meeting, webinar, or workshop held by the committee.

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[7] The workshop was supported by the USDA Biotechnology Risk Assessment Grants program.

[8] The names of all speakers and the agendas for the in-person meetings and webinars are in Appendix C. The speaker names and agenda for the workshop are in Appendix D. No speakers were compensated for their presentations; however, the National Academies offered to pay all relevant travel expenses for all speakers invited to the in-person meetings. When prior commitments prevented an invited speaker from attending an in-person meeting, accommodations were made to connect the speaker to the meeting via the Internet. Appendix E contains a list of invited speakers who were unable to present to the committee at public meetings or via webinar because of other commitments, who declined the committee's invitation, or who did not respond to the committee's invitation.

[9] Several members of the committee also attended a National Academies workshop organized by the Roundtable on Public Interfaces of the Life Sciences. The workshop, When Science and Citizens Connect: Public Engagement on Genetically Modified Organisms, was held in January 2015.

[10] Recordings of the committee's meetings, webinars, and the workshop are at http://nas-sites.org/ge-crops/. Accessed November 23, 2015.

TABLE 1-2 Topics Presented at the Committee's Public Meetings and Webinars

Event	Date	Topics
Public Meeting 1	September 15–16, 2014	Research on public perceptions and understanding of genetic-engineering technology Perspectives on the U.S. regulatory system for genetically engineered (GE) crops, in terms of both unnecessary restrictions and lax oversight Consolidation of corporate ownership in the U.S. seed sector Perspectives on corporate influence on agricultural research at public institutions Critiques of genetic engineering in agriculture with regard to its usefulness in meeting world food demands and distributing benefits equitably to resource-poor farmers and low-income consumers Health and environmental risks related to GE crops and foods
Webinar 1	October 1, 2014	Perspectives on GE crops from agricultural extension specialists in different crop-production regions of the United States
Webinar 2	October 8, 2014	International trade issues related to GE crops
Webinar 3	October 22, 2014	Perspectives on GE crops from agricultural extension specialists in different crop-production regions of the United States
Webinar 4	November 6, 2014	GE disease resistance in crops, specifically in papaya, plum, cassava, and potato
Public Meeting 2	December 10, 2014	Emerging technologies and synthetic-biology approaches to GE crops U.S. regulatory system for GE crops Perspectives on genetic engineering in agriculture from representatives of large GE seed-producing companies
Webinar 5	January 27, 2015	The state of plant-breeding research in public research institutions
Webinar 6	February 4, 2015	Social-science research on GE crop adoption and acceptance
Webinar 7	February 26, 2015	Synopsis of the 2004 National Research Council report, *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects*

TABLE 1-2 Continued

Event	Date	Topics
Public Meeting 3	March 5, 2015	U.S. regulatory system for GE crops with regards to assessment of the safety of GE foods Responsibilities and operating process of the European Food Safety Authority Methods for evaluating the risk of allergy from GE foods State of knowledge about potential perturbations of the gastrointestinal tract mucosa by GE foods State of knowledge about metabolomic analysis to confirm the effects of transgenesis in plants
Webinar 8	March 19, 2015	Socioeconomic issues related to GE crops in developed countries
Webinar 9	March 27, 2015	GE trees
Webinar 10	April 6, 2015	State of knowledge about the interaction between GE crops and the human gut microbiome
Webinar 11	April 21, 2015	GE quality traits, specifically in apple, potato, and alfalfa
Webinar 12	April 30, 2015	Practices and priorities of donor organizations involved in agricultural development with respect to GE crops
Webinar 13	May 6, 2015	Intellectual-property rights issues related to GE crops
Webinar 14	May 7, 2015	Prospects for, risks posed by, and benefits of the use of RNA interference in crop production
Webinar 15	May 13, 2015	Socioeconomic issues related to GE crops in developing countries

Input from the Public

As with all National Academies committees, members of the public were invited to provide oral or written statements and information to the committee. The in-person meetings held in Washington, DC, in September 2014, December 2014, and March 2015 included time for members of the public to provide comments to the committee. Persons who chose to speak could do so in person or via teleconference. Recordings of the public-comment sessions were archived on the study's website.

The committee also invited members of the public to provide recommendations for invited speakers via the study's website during the information-gathering phase of the study.

Written comments to the committee could be submitted at any point during the study process. Comments and information could be delivered to National Academies staff at committee meetings and via email. Members of the public could also submit comments or upload relevant documents to the study's website. More than 700 comments and documents were submitted to the committee, and the committee read all of them.

The report discusses many topics that were not specifically raised in the public comments, but the committee was tasked to assess the evidence of purported benefits and adverse effects, so it made a concerted effort to address any issues brought up by the public on which it could find evidence. The submitted public comments contained a wide variety of concerns about and hopes for GE crops. Table 1-3 summarizes topics raised in the public comments and shows where they are discussed in the report.

Some commenters told the committee in written statements or at its public meetings that the committee should make a decisive pronouncement endorsing GE crops as categorically beneficial. Others encouraged the committee to denounce the development and use of GE crops strongly. However, an evaluation of GE crops is full of nuance. GE crops encompass many types of GE traits, are grown in countries with differently structured farm sectors and regulatory systems, and, more and more, are created by using one or several genetic-engineering technologies along with conventional plant-breeding approaches. Social and scientific challenges are likely to depend on which crop is being considered or where the crop in question is grown. Given the diversity of issues contained in its task, the committee concluded that sweeping statements would be inappropriate. Instead, it engaged with each issue presented to it and explored the available evidence. The committee urges the reader to undertake a similar process of engagement with the text on any issue listed in Table 1-3 (and more extensively in Appendix F) that may be of personal or professional importance.

Assessing the Quality of the Evidence

To evaluate the evidence on purported benefits of and risks posed by GE crops, the committee drew on information presented during public meetings, webinars, and the workshop. After presentations, the committee commonly made requests to invited speakers for additional data or documentation. It also reviewed statements and articles that were submitted or referred to by speakers or members of the public, and it thoroughly consulted relevant peer-reviewed scientific literature.

In its effort to be a trustworthy source of information for all parties interested in GE crops, the committee made a concerted effort to access and evaluate all evidence on each topic covered in its report. On some purported effects of GE crops, there was a great deal of clear evidence

TABLE 1-3 Topics Discussed in Public Comments[a]

Topic	Page number(s)
Agronomic	
Effects of genetic engineering on yield	98–116, 127–133,140
Genetic diversity in crop varieties	143–146
Environment	
Biodiversity in farms and fields	141–143
Coexistence of genetically engineered (GE) and non-GE crops	296–302
Effects on environment	140–154
Effects on herbicide use	133–135
Effects on insect and weed resistance	122–126, 136–139
Effects on insecticide use	116–121
Effects on landscape biodiversity	146–154
Human Health and Food Safety	
Appropriate animal testing	184–198
Regulatory actions by the U.S. Food and Drug Administration	184–207, 466–477
Health effects of herbicides associated with herbicide-resistant crops	212–213, 231–233
Health effects of insect-resistant crops	179–225, 231–233
Health effects of RNA-interference technology	233–235
Sufficiency of health testing	176–207
Economic	
Costs of regulation	310–316
Costs of research and development	310–316
Effects on farmers in developed and developing countries	256–302
Effects on global markets	306–310
Socioeconomic effects in developing countries	271–287
Public and Social Goods	
Farmer knowledge	288–291
Feeding the growing world population	331–333, 437–442
Seed saving	318–319
Access to Information	
Data quality and comprehensiveness	171
Intellectual property	316–331
Regulation of GE crops	456–493
Transparency in data reporting	502–506

TABLE 1-3 Continued

Topic	Page number(s)
Scientific Progress	
Effects of debate about genetic engineering	310–316
Regulation of genome editing	493–500

[a] All submitted comments and documents were added to the study's public-comment file, which was and is available on request from the National Academies' Public Access Records Office. Requests can be directed to PARO@nas.edu.

from diverse sources; on others, evidence to assess a purported effect was lacking or inconclusive. The committee attempted to assess the degree of uncertainty surrounding evidence regarding effects covered in its report. The committee was also cognizant of the fact that the effect of a GE crop or accompanying technology depends on the specific social, environmental, and economic context into which it is introduced, and the committee addressed this heterogeneity whenever possible.

REPORT REVIEW PROCESS

The concluding phase of a National Academies report is the review process. When a draft report is complete, it is submitted to the National Academies' Report Review Committee. The Report Review Committee recruits a diverse and critical group of reviewers who have expertise complementary to that of the committee to ensure that critical gaps and misinformation are identified. The reviewers are anonymous to the committee during the review process, and their comments remain anonymous after the report is published (see Acknowledgments of Reviewers). Reviewers are asked to assess how well a report addresses a study's statement of task. The committee must respond to each of the comments received and submit a point-by-point explanation of its reasoning to the Report Review Committee. When the Report Review Committee decides that the committee has adequately and appropriately addressed the reviewers' comments, the report is ready to be released to the public and to the sponsors.

ORGANIZATION OF THE REPORT

Examining the purported benefits of and risks posed by GE crops—past and future—in the linear structure of a report is challenging because many effects change over time with the evolution of genetic engineering and the manner in which it is used. Effects also overlap social, economic, and environmental boundaries. Conducting a broad investigation of the spatial effects of GE crops is an additional challenge in that the scale and degree of mechanization of farms and the kinds of crops produced vary greatly around the world. Nevertheless, the committee strove to be comprehensive in its review of the purported benefits and risks and looked at their effects inside and outside the United States. It also sought to be thorough in its examination of the opportunities afforded and the challenges raised by emerging genetic-engineering technologies.

Chapter 2 provides a framework for the report. It discusses the committee's approach to the assessment of risks and benefits, reviews what is known about public attitudes about GE crops, introduces the concepts and actors involved in the governance of genetic engineering in agriculture, and defines some of the terms used in the report.

The next four chapters address the "experience" task of the committee's charge. Chapter 3 reviews the development and introduction of GE crops, including a brief primer on the mechanism of recombinant-DNA technology and how plants were initially transformed through genetic engineering. It lays out the kinds of crops and traits that have been commercialized and where they were grown in 2015, and it provides a synopsis about GE crops that were not commercialized or that have been withdrawn from the market. It concludes with a brief introduction of regulatory approaches to GE crops. The economic, environmental, and social effects of GE crops are discussed in the next three chapters. Chapter 4 addresses the agronomic and environmental effects. Chapter 5 examines mechanisms for testing the safety of GE crops and foods derived from GE crops in the United States and other countries. It also discusses the purported risks and benefits associated with GE crops and foods related to human health, such as nutritional effects, insecticide and herbicide use, allergens, gastrointestinal tract issues, disease, and chronic illnesses. Chapter 6 deals with the complex issues of social and economic benefits and risks.

Chapters 7 and 8 respond to the committee's tasks related to "prospects." Chapter 7 summarizes emerging genetic-engineering approaches, a few of which are already being used to develop crops for commercial production, and assesses the utility (as of 2015) of "-omics" technology to detect alterations in plant genomes. Chapter 8 describes a number of new traits that were in development for GE crops in 2015 and discusses how they relate to sustainability and food security in the future.

Chapter 9 describes the existing international governance frameworks and compares the regulatory systems in place for GE crops in the United States, the European Union, Canada, and Brazil. It also evaluates the applicability of current regulatory systems to emerging genetic-engineering technologies and offers several general and specific recommendations regarding the U.S. regulatory system.

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The Framework of the Report

The committee finds it important at the outset to lay some groundwork for its report. In this chapter, the committee explains its approach to risk and benefit assessment in light of previous National Research Council work in the field and in the context of the general public's familiarity with genetically engineered (GE) crops, describes the concepts and actors involved in the governance of genetic-engineering technology in agriculture and how their diverse goals can be balanced or otherwise accommodated, and discusses some of the terms that are commonly used in the report. Additional terms are in the report's glossary (Appendix G).

THOROUGH ASSESSMENT OF AN UNFAMILIAR ISSUE

Analysis of risks and benefits associated with a technology is often considered to involve the difficult but straightforward scientific task of reviewing the most relevant and highest-quality scientific papers on the technology and drawing up a set of statistically supported conclusions and recommendations. However, in 1996, the National Research Council broke new ground on risk assessment with the highly regarded report *Understanding Risk: Informing Decisions in a Democratic Society*, which pointed out that a purely technical assessment of risk could result in an analysis that accurately answered the wrong questions and would be of little use to decision-makers. It outlined an approach that balanced analysis and deliberation in a manner that was more likely to address the concerns of interested and affected parties in ways that earned their trust and confidence. The process in 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 critical outcome of such a risk characterization is a synthesis of the evidence relevant to the critical questions, including the state of knowledge and the state of uncertainty regarding that knowledge (NRC, 1996).

The present report focuses on both benefits and risks, but the perspectives outlined in the 1996 National Research Council report (and later work in risk assessment, such as NRC, 2009) were relevant to the committee's approach to its statement of task. Although the goals set out in *Understanding Risk* are theoretically appealing, achieving them is difficult. The committee worked toward the goal of asking the most relevant questions through early engagement with people and groups that held opposing views of GE crops and foods derived from them. Persons who had deep concerns about the adverse health, environmental, social, and economic effects of GE crops and persons who were enthusiastic about substantial benefits afforded by GE crops were invited to speak to the committee starting at its first meeting.[1]

It was clear from that early engagement—and from many presentations and public comments that the committee received later—that opinions on GE crops and food derived from them span the spectrum from extremely risky to overwhelmingly beneficial and that many members of the public hold extremely negative or extremely positive views of GE crops. However, public-opinion surveys in the United States reveal that most Americans do not know much about genetic engineering as it is related to agriculture. The level of awareness has not changed much over time. Throughout the 1990s, a number of surveys reported that at least 50 percent of respondents said that they knew "not much" or "nothing at all" about genetic engineering involved with crop plants (Shanahan et al., 2001). By 2014, awareness levels were still low, with only 40 percent of respondents claiming to have heard or read at least "some[thing]" about genetic engineering despite widespread adoption by U.S. agricultural producers and the existence of many food products that contained GE ingredients (Runge et al., 2015); close to 30 percent of the U.S. public had not read or heard anything on the topic.

Even if levels of awareness about genetic engineering in agriculture have stayed low in the United States, it is clear that the proportion of Americans who believe that foods derived from GE crops pose a serious health hazard to consumers has steadily increased, from 27 percent in 1999 to 48 percent in 2013 (Runge et al., 2015). However, 69 percent of Americans indicated in 2014 that they were likely or somewhat likely to buy produce derived from genetic-engineering techniques if it meant that fewer pesticide applications were required for food production.

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[1] See Appendix C for the first meeting's agenda.

Data from other countries reveal a variety of public reactions to GE crops. Argentina (one of the major growers of GE crops) has yet to see sizable public opposition to the use of the technology in agriculture (Massarani et al., 2013). In Brazil, however, farmers widely adopted the technology although strong public opposition was present (Brossard et al., 2013); thus, magnitude of adoption by farmers does not always represent public opinion in a specific country. In other countries, GE crops have been blocked on the basis of public opinion and have never been released. For instance, Swiss citizens voted in 2005 in favor of a 10-year moratorium on GE plants and animals in agriculture in spite of robust opposition from the Swiss government, industry, and the scientific community (Stafford, 2005). Widespread resistance to genetic engineering in European countries (Gaskell et al., 2006) also may be driving resistance in countries that export to Europe.

The extent of knowledge about genetic engineering in general or about a specific application of the technology does not solely predict public support or rejection; indeed, the so-called knowledge-deficit model has been discredited by social-science research (Allum et al., 2008). Instead, individuals often rely on cognitive (thought-process) shortcuts to make sense of a complex issue like genetic engineering, and mass-media content—which is shaped by active stakeholders groups—has often provided these shortcuts (Scheufele, 2006). Social scientists have pointed out that social psychological processes that explain public attitudes toward genetic engineering are complex and go beyond understanding the science behind the technology; well-established individual beliefs, such as religious beliefs or deference to scientific authority, can act as perceptual filters when complex information is processed and, as a result, two persons may interpret the same mass-media information differently and reach conflicting conclusions regarding the technology (Scheufele, 2006; Brossard and Shanahan, 2007). At the same time, perceptions of the risks related to a technology are society-, culture-, and context-specific (Slovic, 2000). It is therefore understandable that public opinions of genetic engineering have included a large spectrum of attitudes because they depend on local sociopolitical and cultural context, the information climate (including the nature of mass-media coverage), and a person's individual characteristics, such as worldview, level of trust in the systems in place, and other psychological aspects (Nisbet and Scheufele, 2009; Figure 2-1).

Given the context specificity and complexity of public opinions of genetic engineering, the committee cautions against a straightforward comparison of public-opinion data on GE crops among countries; often the methods used to gather the data are dissimilar and survey questions are phrased or interpreted differently in different languages. In many instances, conclusions lack generalizability because of sampling issues. Reliable public-opinion data from Africa have yet to be published and Asian

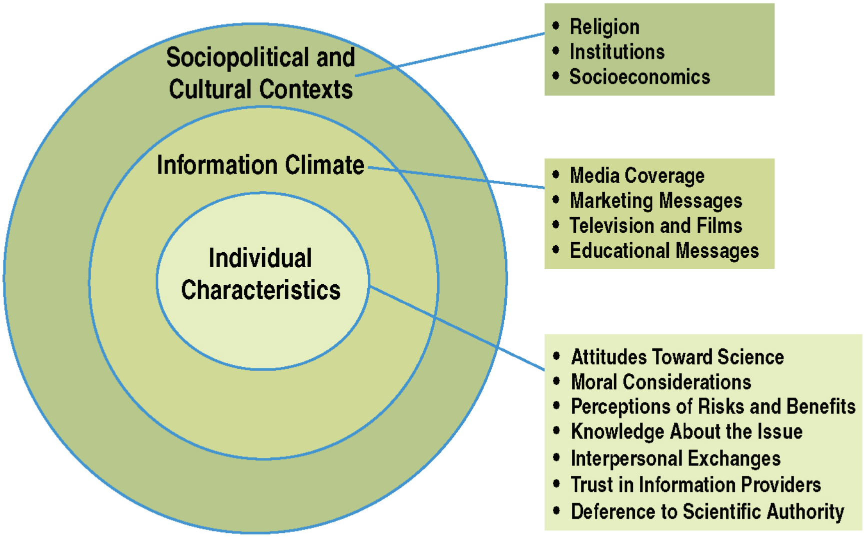

FIGURE 2-1 Contextual filters that influence a person's perception of scientific innovations.
SOURCE: Work of D. Brossard, cited in NRC (2015b).

data yield conflicting results. What is clear is that public awareness about genetic engineering as a process and about the potential applications of genetic engineering has remained low around the globe since the introduction of commercial GE crops in the mid-1990s. When articulated, support of or opposition to genetic engineering in different countries has fluctuated widely, depending on the country, the timeframe, and the cultural and informational context (Brossard, 2012); controversies around GE crops have unfolded differently around the world.

Keeping in mind the analytic–deliberative process described in *Understanding Risk*, the committee has done its best to consider "alternative sets of assumptions that may lead to divergent estimates of risk [and benefits]; to address social, economic, ecological, and ethical outcomes as well as consequences for human health and safety; and to consider outcomes for particular populations in addition to risks [and benefits] to whole populations, maximally exposed individuals, or other standard affected groups" (NRC, 1996:3).[2] As set out in *Understanding Risk*, the purpose of risk characterization is to "describe the potentially hazardous situation in as accurate, thorough, and decision-relevant a manner as possible, addressing

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[2] The committee has made the additions in brackets.

the significant concerns of the interested and affected parties, and to make this information understandable and accessible to public officials and to the parties" (NRC, 1996:2). The committee believes that accurate and thorough characterization applies as much to benefits as it does to risks, and it has striven to describe the risks and benefits associated with GE crops in a manner that balances detail and makes its analysis accessible to a broad audience.

The committee sought to write a report that would help readers to evaluate for themselves the dimensions of the debate around the use of genetic engineering in agriculture that were aired at the committee's first meeting and in many submitted public comments (see Table 1-3). Points of view among people already familiar with GE crops are split on such topics as the effect of these crops on the environment (Chapter 4) and the implications of GE crops and their accompanying technologies for human health (Chapter 5). There is also disagreement about the risks and benefits for farmers who grow various GE crops and the effects of adoption on communities in rural areas and developing countries (Chapter 6). Issues of ownership of and access to technology are also debated (Chapter 6). Ethical considerations about consumers' right to know whether their food was derived from GE crops (Chapter 6) and the adequacy of safety assessments of genetic engineering (Chapters 5 and 9) are also points of dispute. The committee's goal has been to examine the evidence that bears on those issues.

GOVERNANCE OF GENETICALLY ENGINEERED CROPS

The terms *regulation* and *governance* are sometimes used interchangeably, but regulations are only a subset of the factors involved in governance of technologies (Kuzma et al., 2008). In line with previous National Research Council reports, the committee understood governance to refer to any institutional arrangement that attempts to shape an individual's or organization's behavior (NRC, 2005, 2015a). In laying out the framework of its report, the committee was aware of the multitude of actors that contribute to the governance of genetic engineering in agriculture. The committee highlights here the tradeoffs involved in any structure of governance of GE crops.

Governance Actors

Busch (2011) noted that the food network of the 21st century—of which GE crops and food are parts—is "governed by a plethora of public and private standards" in which a wide array of actors[3] participate. That

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[3] *Actor* is a social scientific concept used to refer to individuals or collective entities (for example, government agencies, firms, retail groups, nonprofit organizations, and citizens) when their behavior is intentional and interactive.

is, no single institutional arrangement shapes the governance of food in general or GE crops in particular. Indeed, the committee identified a number of institutions that attempt to exert influence over farmers, consumers, and each other in the realm of GE crops.

Regional,[4] national, and subnational governments and tribal governments in the United States shape behavior in many ways, including regulations, incentives, and funding. For example, governments issue permits for testing new GE crops or traits, which may be accompanied by conditions regarding confinement and post-trial monitoring. Governments promulgate laws and regulations that require safety assessments of GE crops. They may create intellectual-property rules that protect GE crop inventions. To the extent that private intellectual-property or contractual disputes or tort actions arise with respect to GE crops, governments are involved through the court systems that adjudicate those actions. Governments can also be a source of research funding for GE crops.

Upstream private, for-profit companies—such as ones that develop GE traits and incorporate them into crop varieties—also fund research. Their goal is to develop a commercial product, something government-supported projects may or may not target. Furthermore, the companies develop and acquire intellectual property and defend it from infringement. They enforce technology-use agreements (contracts) with farmers of GE crops in which farmers agree not to use seeds from the harvest of GE crops to plant the following year's crop. The companies also recoup a technology-use fee from farmers for the GE trait in crops.

Downstream companies—those closer to the food consumer, such as food manufacturers and retailers—exert their influence by setting standards. That practice has become a strong force of governance in the global agrifood system in general (Reardon and Farina, 2001; Hatanaka et al., 2005; Henson and Reardon, 2005; Fulponi, 2006; Bain et al., 2013). However, private standard-setting is not the domain only of for-profit companies. Many nongovernmental organizations (NGOs) also set standards, and private standards developed by manufacturers, retailers, and NGOs exist alongside the regulatory standards of governments. Although they are rarely legally binding, private standards have often de facto become mandatory for suppliers (Henson and Reardon, 2005; Henson, 2008). Examples pertaining to GE crops are a food manufacturer that does not allow ingredients made from GE crops and an NGO that acts as a third-party certifier to ascertain that a product is not made with any GE crops. The effects of private standards may reach far upstream, influencing whether a GE seed developer decides to introduce a particular trait into the market.

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[4] The European Union is a regional government.

Standard-setting can also take place at the international level. For example, the Organisation for Economic Co-operation and Development influenced the environmental assessment of GE crops through the early development of guidelines (OECD, 1986). No central international authority governs all facets of food production and consumption (Busch, 2011), but the Codex Alimentarius Commission sets nonlegally-binding standards for assessing the safety of foods derived from GE crops (CAC, 2003a,b). Many countries make use of the Codex standards in developing scientific risk assessment of food safety and in shaping their national regulatory systems.

International trade agreements, such as those overseen by the World Trade Organization (WTO), also affect policies on GE crops. The WTO's Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) governs measures to protect human, animal, or plant life or health, including food safety. While acknowledging the right of governments to enact such measures, the SPS Agreement recognizes that the measures can operate as a de facto trade barrier and therefore sets requirements to minimize trade barriers. Among other things, the SPS Agreement requires measures to be based on scientific principles and not maintained without scientific evidence except when scientific information is insufficient. In such a case, a country may proceed to regulate but must also seek to resolve the scientific uncertainty.

International agreements are not restricted to the economic issues of trade; they may also try to influence the effects on the environment of GE crops. The 2000 Cartagena Protocol on Biosafety (Biosafety Protocol), developed under the 1992 Convention on Biological Diversity, addresses potential environmental concerns that might be posed by introducing "living modified organisms," such as GE seeds or plants that could propagate, into countries through international trade. The Biosafety Protocol expressly adopts a precautionary approach that allows countries to deny the importation of a GE product if they consider that there is not enough scientific evidence that the product is safe. It also permits countries to consider socioeconomic issues.

Other institutions are also involved. They include foundations that allocate funds for research or advocacy and educational institutions that conduct basic or applied research in genetic engineering.

More amorphous institutions, such as consumer movements, also have influence. Social and civic movements that address food and agriculture are not new, but their diversity and visibility have grown dramatically since the 1990s (Hinrichs and Eshleman, 2014). A wide array of issues are captured by the broad categorization of "agrifood movements,"[5] including environmental and organic-food issues, farmers' markets, food justice, anti-GE crops, and animal welfare. Scholars have identified many reasons for agrifood movements to have expanded, including concerns about environmental degradation, a lack of trust in the safety of the system, an effort to regain a sense of power and control by knowing more about who grows one's food, a desire to align one's values with the food one eats, and a growing moral questioning of mainstream consumption habits (Nestle, 2003; Morgan et al., 2006; Hinrichs and Eshleman, 2014).

A final element of governance is related to transparency and public participation with respect to various aspects of GE crops. Some of the relevant rules are formal, such as international human-rights laws that require access to information and public participation in international human-rights institutions and freedom-of-information laws in national governments. Other rules are informal, such as corporate practices related to the release of information.

Clearly, the field of governance of GE crops has many actors. They interact with and influence each other. For example, some NGOs work to mobilize consumer opinion, affect the allocation of research funding related to GE crops, and influence the formulation, implementation, and monitoring of national laws and regulations. Researchers—whether employed by a national government, a private seed company, or an educational institution—are affected by government regulations. With the growth of agrifood movements, other actors in the global food system, particularly food retailers, have taken notice and modified their own policies and practices either in response to or in anticipation of consumer demands. Studies have shown that private standards shape government policies and can affect practices at the farm level (Gruère and Sengupta, 2009; Tallontire et al., 2011).

Thus, the governance of GE crops is complex, multilayered, and multi-institutional and involves varied binding and nonbinding norms by multiple actors (Paarlberg and Pray, 2007). In theory, many forms of governance allow opportunities for increased participation by diverse actors that represent the state, the market, and civil society. In practice, harmonizing the various forms of governance is challenging.

Balancing Governance Goals

To create order for the various actors, balance must be struck among competing governance goals. In the literature on governance (for example,

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[5] *Agrifood movements* refers to "a broad field of social action that can be seen as challenging the status quo of the now-prevailing agrifood system" (Friedland, 2010, cited in Hinrichs and Eshleman, 2014:138).

Gisselquist, 2012a,b), the committee identified salient governance goals—such as accuracy, integrity, efficiency, and transparency—that must be balanced or otherwise accommodated with respect to GE crops.[6]

Similar to the process of assessing risk described earlier in the chapter, GE crop governance structures should have credible and acceptable means of determining the accuracy, content, and relative importance of information that is used in decision-making and of taking into account all relevant facts and circumstances. Those goals can be in tension with the goal of regulatory efficiency, that is, the ability of regulatory agencies to make decisions within a reasonable time frame. Decision-makers naturally tend to want all possible relevant information, but providing and obtaining that information involves cost and time. As a practical matter, regulatory agencies must balance their desire for accurate and complete information with the need to make decisions in light of the information that is obtainable in a timely manner and within the resources available to them.

The necessity for transparency and public participation is established by international human-rights law in general (for example, Article 19 of the Universal Declaration of Human Rights) and has been recognized by earlier National Research Council reports, not only in *Understanding Risk* (NRC, 1996) but specifically regarding GE crops and other GE organisms (NRC, 2002, 2004). In many instances, "public participation" as related to governance is a vague concept that encompasses many types of formal engagement mechanisms (from public-opinion surveys to consensus conferences) that have different degrees of relevant stakeholder input and effective consensus-building (Rowe and Frewer, 2005). The structure should operate in a context that allows open and reflexive discussion, that is, makes it possible for the actors to redefine their interests through an iterative process to arrive at new perceptions of the problems that they are seeking to resolve (De Schutter and Deakin, 2005; Irwin et al., 2013). The process is particularly important for such issues as GE crops because of their multidimensionality, their complexity, and the opposing views that engaged stakeholders hold on questions that often transcend the pure scientific realm. The structures should be designed to make sure that there is a level playing field so that well-financed stakeholders' voices do not drown out the voices of less well-financed ones. Moreover, the goal of full

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[6] Other qualities may also be relevant to governance, depending on the approach taken and definitions used. The U.S. Environmental Protection Agency's risk characterization policy, for example, states that "'risk characterization should be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency'" (EPA, 2000:14). The committee focused on transparency and public participation because achieving them provides the best opportunity for an accurate database for making decisions, is critical for mediating between different values, and leads to clarity, consistency, and reasonableness.

participation needs to be considered in light of the need for administrative efficiency to ensure that decisions are made in a timely manner.

Transparency refers to the decision-making process and to the information used to make decisions. With regard to government regulations, for example, transparency helps to build trust and confidence when the public can see the data on which the regulators base their decision. Transparency also helps to ensure democratic accountability to ensure that regulators make appropriate decisions that are based on open information. However, rules regarding transparency should take into account the need to protect legitimately confidential business information and national-security concerns.

With regard to transparency and public participation in relation to private-sector governance, the evidence suggests that success has been modest (Fuchs et al., 2011; Box 2-1). There is growing concern over developing and maintaining legitimacy of private governance, which unlike public-sector regulation does not have legitimacy in the authority of the government.

GE crop governance should be sufficiently flexible to take account of changes in relevant considerations and the context in which they exist

BOX 2-1
Participation in Private-Sector Governance

Generally, four types of private-sector governance are relevant to food and agriculture (and therefore to GE crops): individual firms, industry associations, nongovernmental actors, and multi-stakeholder initiatives (MSIs). Of those, MSIs tend to be the most common, and they can include industry, academic, and nongovernmental participants. Roundtables are a type of MSI active in the agriculture and food sector. For example, the Roundtable on Sustainable Palm Oil, the Roundtable on Responsible Soy, and the Roundtable on Sustainable Biofuels all operate to create a standard or set of standards that shape the entire commodity chain, as opposed to other private standards that simply create niche markets (Schouten et al., 2012).

MSIs are seen as more legitimate than other forms of private-sector governance because of the perception that other mechanisms are biased toward particular interests, such as a specific company or industry (Hatanaka and Konefal, 2013), but deficiencies have been found in the operation of the MSIs that have been studied. In a comparative study of food-retail MSIs, civil-society organizations were found to be particularly lacking in representation (Fuchs et al., 2011). A study of an MSI in the United Kingdom that focused on genetic engineering found that “efforts to widen the basis of decision-making [had] led to a much more pronounced exposure of underlying scientific uncertainty, incomplete and contradictory evidence, and contested value positions” (Walls et al., 2005:656), which the authors concluded exacerbated the distrust that the initiative sought to reduce.

(Kuzma, 2014). For example, the structure of regulations should have the capability to respond appropriately to changes in genetic-engineering techniques and capabilities and to change in technologies associated with genetic engineering, societal risk preferences, environmental and social conditions, and scientific understanding. Governance should be able to adapt on the basis of experience. At the same time, both the public and regulated entities need some degree of predictability and stability. In making investment and development decisions, for example, companies need to have a reliable estimate of the process and standards under which they will need to get approval if they are to get a product to market. Similarly, farmers need to have a reliable sense of what types of products are likely to be available.

Finally, ideally and broadly speaking, governance of GE crops should facilitate achieving the maximum societal benefits from GE crops at given levels of acceptable risk. Alternatively, one could speak of a goal of minimizing the governance resources[7] necessary to achieve given levels of societal risks and benefits associated with GE crops. It is necessary to consider levels of acceptable risk in the plural, rather than just one, because risks posed by GE crops vary according to the nature, likely use, and intended location of the GE crop in question. For example, risks related to biodiversity, economic conditions in rural areas, and food safety differ among GE crops, or, more specifically, among GE traits. The same is true with respect to the benefits to be derived from GE crops or traits. For the same reasons, the goal of achieving the maximum societal benefits from GE crops at given levels of acceptable risk cannot be sought in any precise manner; rather, the goal provides a framework for thinking about governance in the context of GE crops.

GE crop governance involves a dynamic iterative and interactive process between those governing, those being governed, and other elements of society. That is similar to the analytic–deliberative process outlined in *Understanding Risk* for assessing risks and benefits (NRC, 1996). In later chapters of the present report, the committee attempts to characterize the risks and benefits related to GE crops and to explain the balances and tradeoffs inherent to the governance of genetic-engineering technology.

TERMINOLOGY AND ITS CHALLENGES

As they embarked on addressing their statement of task, the committee members needed to agree on the definitions of terms that would be used in the report. Terms related to genetic engineering are sometimes used in sci-

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[7] Minimizing use of governance resources might involve a variety of approaches, including changes in the number or type of regulations, enforcement methods, or roles of actors involved in governance.

entific and lay literature to mean different things. Therefore, the committee spent considerable time discussing terminology and definitions.

Terms

The committee started by defining what it meant by *crop* because the bounds of the term affected the scope of the study's statement of task. In this report, *crop* refers to vascular plants that are grown for subsistence, environmental enhancement, or economic profit. Vascular plants contain water-conducting and nutrient-conducting tissues. Under those constraints, bacteria, algae, and animals were not considered. Along with food crops, ornamental and nursery plants were included in the committee's task, as were trees, which may be produced for economic returns but may also be planted and proliferate in unmanaged ecosystems.

In the report, *genetic engineering* means the introduction of or change to DNA, RNA, or proteins manipulated by humans to effect a change in an organism's genome or epigenome.[8] *Genome* refers to the specific sequence of the DNA of an organism; genomes contain the genes of an organism. The *epigenome* consists of the physical factors that affect the expression of genes without affecting the DNA sequence of the genome. The committee's definition of *genetic engineering* includes *Agrobacterium*-mediated and gene gun-mediated gene transfer to plants (described in Chapter 3) as well as more recently developed technologies such as CRISPR, TALENs, and ZFNs (described in Chapter 7). *Recombinant DNA* is a DNA molecule that is created by laboratory manipulation and that joins two or more segments of DNA that would not be found joined in nature.

Making sexual crosses of plants that have different genomes, selecting desirable plants to serve as parent lines, and changing (mutagenizing) the genome with chemical methods or irradiation are considered *conventional plant breeding*, which does not include *genetic engineering*. Marker-assisted selection (MAS) is included in *conventional breeding*. MAS involves the use of in vitro–manipulated nucleic acids on samples of extracted DNA to determine which plants or other organisms have particular versions of existing genes. The markers do not become part of the plant's genome.

The committee defines *biotechnology* to mean methods other than selective breeding and sexually crossing of plants to endow organisms with new characteristics. Thus, *biotechnology* as used in this report includes

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[8] The term *genetically modified* is often used synonymously with *genetically engineered*. However, the committee kept its terminology consistent with previous National Research Council reports (NRC, 2004, 2010); *genetically modified* is more general and refers to the full array of methods that are used to alter the genetic composition of an organism, including conventional plant breeding.

some types of conventional breeding, such as the use of mutagenesis to alter a genome and the use of in vitro–culture techniques to enable embryos derived from wide crossing to be viable.

A *transgene* is any gene transferred into an organism by genetic engineering. In this report, however, a *transgenic organism*[9] is specifically an organism that has had genes that contain sequences from another species or synthetic sequences introduced into its genome by genetic engineering; this definition distinguishes a transgenic organism from a cisgenic or intragenic organism (described below), all of which contain transgenes. A *transgenic event* is a unique insertion of a transgene into a genome. When a plant transformation experiment is performed, many independent transgenic events are selected from tissue culture. The transgenic event is the subject of regulatory approval in most systems.

Cisgenesis involves genetically engineering a recipient plant with an endogenous gene from a sexually compatible plant, that is, a transfer that could be accomplished by conventional breeding. In cisgenesis, an entire endogenous gene is cloned intact from a plant that is sexually compatible and is inserted into the crop's genome. In *intragenesis*, various plant DNAs, all of which come from varieties of the crop or sexually compatible relatives, are combined into a gene delivery cassette and then inserted.[10] Cisgenic and intragenic organisms thus may have transgenes, but they are not transgenic.

Challenges in Defining Terms

A major challenge in defining terms is that nature does not exist in neat boxes. For example, the commonly used definition of cisgenesis noted above is based on whether a genetically engineered recipient plant receives a gene from a sexually compatible plant. However, the criterion of sexual compatibility does not necessarily indicate the precise relatedness of two plants. In many cases, a version (allele) of a single gene creates sexual incompatibility in plants (Bomblies, 2010; Rieseberg and Blackman, 2010). In principle, plants that are not sexually compatible could have identical genomes except for one version of one gene. Furthermore, there often is no clear demarcation point that indicates when a genome becomes sufficiently different from another genome to indicate that a separate species designation is warranted. Thus, although moving genes from one species to another

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[9] The term *transgenic* is sometimes used to include an organism in which genetic material from another species has transferred naturally, that is, by events not manipulated by humans. The committee decided not to include such natural transfers in the definition of *transgenic* in this report because of its focus on genetic engineering, which involves human manipulation.

[10] *Cisgenesis* and *intragenesis* are discussed more in Chapter 7.

has been raised as a general concern about GE crops, it is not always clear whether related organisms are different species.

It is important to note that genomes often contain DNA that has been introduced from distantly related organisms during the process of evolution. Such cases of natural gene transfer (that is, not from human manipulation) are known as horizontal gene transfer. For example, sweet potato (*Ipomoea batatas*) naturally contains genetic material from the bacterium *Agrobacterium rhizogenes* (Kyndt et al., 2015) and some sea slugs contain DNA from algae (Rumpho et al., 2008).

Another challenge is posed by the fact that human ingenuity also is not confined to neat boxes, and technological developments have enabled multiple routes to a similar end with respect to plant genetic modification. For example, a process known as TILLING (targeting induced local lesions in genomes, described in Chapter 7) is an alternative to genetic engineering for creating plants that have specific changes in specific genes (Henikoff et al., 2004). TILLING does not involve genetic engineering according to the definition above (or the definition used by most regulatory agencies), but it may create changes throughout a genome that would not occur if the same changes in a gene were created by genetic engineering.

CONCLUSIONS

The rapid technological development of new methods to modify genomes, such as CRISPRs, will continue to present both definitional and analytic challenges. The purpose of this chapter has been to introduce the complexity of the landscape in which GE crops exist and genetic engineering occurs. Many stakeholders who have diverse opinions act at local, national, regional, and international levels. They often struggle to communicate with one another about a scientific process that is evolving and that has social, environmental, economic, and possibly health effects. The committee's statement of task charges it to address food-safety, environmental, social, economic, regulatory, and other aspects of GE crops, and it does so. However, as is evident in this report's later chapters, the technologies, traits, and contexts of deployment of specific GE crop varieties are so diverse that generalizations about GE crops as a single defined entity are not possible.

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3

Genetically Engineered Crops Through 2015

Having laid the groundwork for its approach to risk and benefit assessment, introduced the major actors operating in the sphere of governance of genetically engineered (GE) crops, and defined the terms commonly used in its report, the committee turns in this chapter to its first charge in the statement of task: an examination of the history of the development and introduction of GE crops, both in and outside the United States. The examination includes not only GE crops that were available in 2015 but GE crops that were developed but not commercialized, GE crops that entered the market but were withdrawn or discontinued, and crops with GE traits that were developed and near market release as of 2015. It also gives an introduction of the government processes that have emerged to regulate GE crops.

THE DEVELOPMENT OF GENETIC ENGINEERING IN AGRICULTURE

People have been domesticating plants for at least 10,000 years. Early plant domestication involved selecting individual plants, fruits, seeds, inflorescences, or other propagules for characteristics of interest. Selected characteristics (traits) included higher yields, reduced toxicity, improved flavor or morphology of seeds or fruits, and seed heads (in grains) or pods (in legumes) that did not shatter and were therefore easier to harvest. Selection permitted people to domesticate numerous wild plants into crops, such as wheat (*Triticum aestivum*), rice (*Oryza sativa*), maize (*Zea mays*), potato (*Solanum tuberosum*), and tomato (*Solanum lycopersicum*).

One of the most vivid examples of domestication is maize (corn). Beginning some 6,000–10,000 years ago, ancient Meso-American farmers drastically changed teosinte (*Zea mays* subsp. *parviglumis*) through selection (Figure 3-1). Teosinte is a grass species that has numerous lateral branches and cobs with 5–12 individually encapsulated kernels that drop to the ground when ripe. Through human selections based on very rare, desirable attributes caused by naturally occurring mutations, a plant was derived with no lateral branching (that is, a single stalk) and a cob with dozens or even hundreds of large seeds (kernels) that were encased in husk leaves; this resulted in the maize that is grown today (Doebley, 2004; Flint-Garcia, 2013; Wang et al., 2015).

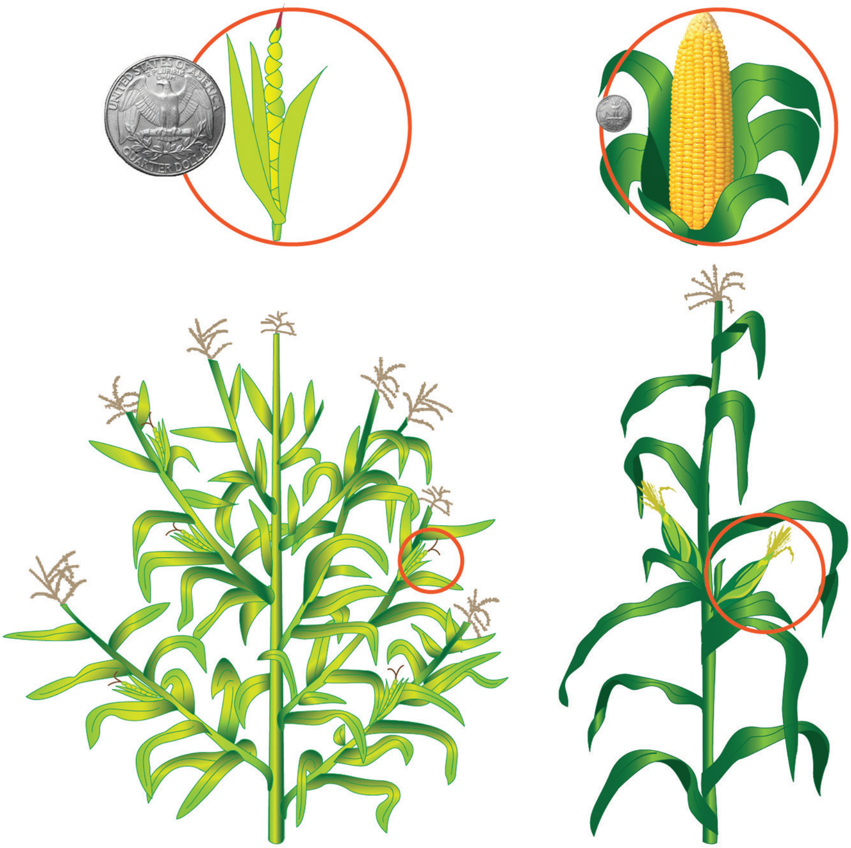

FIGURE 3-1 Effects of human selection and domestication of teosinte (left) that yielded maize (right).
SOURCE: Based on Fuller (2005).
NOTE: The U.S. quarter coin is included for scale (about 2 centimeters in diameter).

Domestication of wild *Solanum* species native to the American continents through the selection of altered fruit size, fruit shape, seed size, and taste led to the tomato (Bai and Lindhout, 2007); wild tomatoes are generally neither large nor tasty. The progenitors of carrot (*Daucus carota* subsp. *sativus*) were woody, gnarly, and white, rather than tasty, uniformly shaped, and orange. Developed first in France and later in the United States, today's strawberries (*Fragaria* × *ananassa*) descend from hybrids of two species, one of which was prized for its flavor (originally found in what is now the U.S. state of Virginia) and the other for its size (grown off the coast of Chile).

The modern era of genetics and plant breeding can be traced to Darwin's theory of evolution and natural selection and to Mendel's elucidation of the basic principles of heredity in the mid-1800s. The application of the basic principles of heredity to use the genetic variation (biodiversity) available in a species is a cornerstone of plant breeding. Genetic variation arises naturally in a crop from mutation (changes in the DNA sequence of an individual), recombination of the alleles (variants of a gene) in an individual through sexual reproduction, and introgression of new genes or alleles from a donor species.

Research in the late 19th and early 20th centuries led to a better understanding of genetics, and plant breeders applied this knowledge with increasing precision. They deliberately changed the expression of traits in plants by crossing specific parent plants to produce offspring that had the desired traits. They also discovered methods to accelerate the generation and detection of genetic variation, and this led to targeted and more efficient breeding of improved varieties (for review, see Mba, 2013). DNA mutation is relatively rare in nature (Ossowski et al., 2010), but scientists found that they could use chemicals or radiation to induce mutations in DNA at a much greater frequency (Roychowdhury and Tah, 2013) and thereby increase the genetic variation in the species.[1] Natural and human-made mutations are random (in that they can affect any gene), so breeders must evaluate the progeny so that they can discard individuals that have undesirable or even harmful traits and select individuals that have improved characteristics to develop further.

Nearly a century after the discoveries by Darwin and Mendel, Watson and Crick were awarded the 1962 Nobel prize in medicine for discovering the double-helix structure of DNA (Figure 3-2). Holley, Khorana, and Nirenberg received the 1968 Nobel prize in physiology or medicine for deciphering the genetic code related to protein synthesis. Three-base sequences in DNA specify amino acids. These sequences, or "words," form templates

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[1] Ionizing radiation was used to produce several varieties of rice, wheat, barley (*Hordeum vulgare*), and maize (Roychowdhury and Tah, 2013) and the red-fruited Ruby Sweet and Rio Star grapefruits (*Citrus paradisi*) (see http://www.texasweet.com/texas-grapefruits-and-oranges/texas-grapefruit-history/. Accessed September 18, 2015).

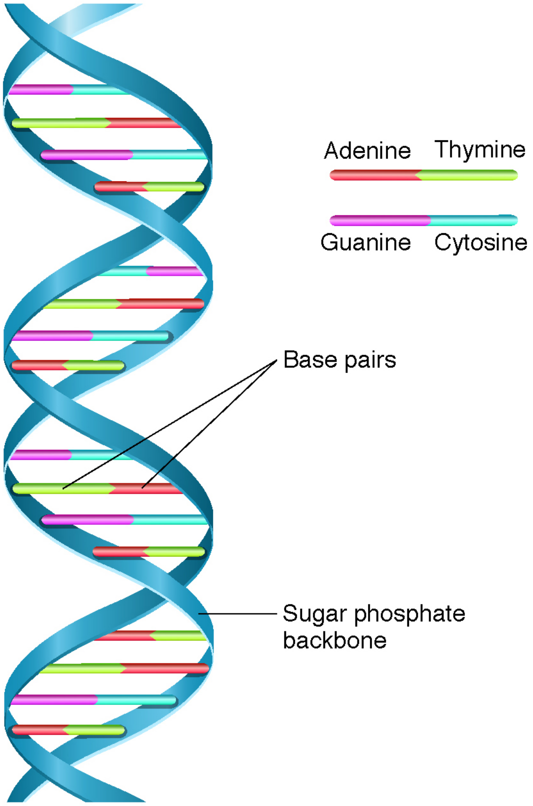

FIGURE 3-2 Structure of DNA.
SOURCE: Based on illustration by the U.S. National Library of Medicine.
NOTE: DNA is a molecule that consists of a chain of nucleotides, which are composed of sugar, phosphate, and one of four bases per nucleotide: adenine, guanine, thymine, and cytosine (A, G, T, and C). The backbone of the molecule is a string of sugar and phosphate. A base—either an A, a G, a T, or a C—sticks out from each of the sugars. The two strands are held together by weak bonds between the bases: A binds with T, and G binds with C. Thus, each strand is complementary to the other.

that align amino acids into specific proteins; genes are long "sentences" of those three-letter "words" (Figure 3-3). In 1973, when Cohen and colleagues described recombinant-DNA (rDNA) techniques that allowed scientists to cut gene sequences from the DNA of one organism and splice them into the DNA of another organism (Cohen et al., 1973), the path was paved for a new approach to increase genetic diversity for use in breeding organisms, including crops: genetic engineering.

The development of GE plants was the product of convergence of several discoveries and technological developments. In addition to the development of rDNA technologies in the early 1970s, genetic engineering in plants required the ability to manipulate plant cells via tissue culture effectively and a fundamental understanding of crown gall disease biology to enable *Agrobacterium*-mediated gene transfer to plants.

Tissue culture is a way to maintain, grow, and manipulate cells, tissues, and organs in vitro. Its use in plants dates at least to 1902 with Haberlandt's research in Germany (Haberlandt, 1902). Plant tissue culture was developed further in numerous laboratories in the first half of the 20th century, and Murashige and Skoog (1962) published the recipe for what has become the most used tissue-culture medium in plant biotechnology. Even though the MS (Murashige and Skoog) medium was developed for tobacco (*Nicotiana tabacum*), it proved effective for many plant taxa. By the time of the rDNA revolution in the 1970s, plant biologists were able to manipulate single cells and tissues of tobacco and other species in culture routinely to produce whole plants. Those developments led to the possibility of selecting and regenerating GE plants from GE cells.

Plants regenerated in tissue culture sometimes vary widely in phenotype (appearance) from the source plant and from each other, and the term *somaclonal variation* was established to refer collectively to such phenotypic variation (Larkin and Scowcroft, 1981). Early explanations of somaclonal variation included several types of genetic changes (mutations), but later evidence also pointed to multiple types of epigenetic changes (Neelakandan and Wang, 2012). When mutation occurs, it reduces the efficiency of obtaining useful GE plants.[2] Plant biotechnologists manage that situation by producing a large number of GE parent lines or clones and selecting ones in which gene expression and phenotype are desirable. In cases in which a desirable GE line has unwanted mutations, elite germplasm is not amenable to genetic transformation, or the GE trait is desired in an array of different germplasms, the initial GE plant is crossed into plants with the desired genetic background and the backcrossing process is continued with selection for the introduced DNA until most or all genetic mutations, epigenetic changes, or undesired traits have been removed.

The crown gall story also begins in the early 1900s, when a type of plant tumor was determined to be caused by a specific bacterium, *Agrobacterium tumefaciens*. In the 1940s, the discovery that tumor cells retained tumorous properties in the absence of *Agrobacterium* led to the idea that the bacterium could cause a permanent genetic change in plant cells. The mechanism of the genetic change was elucidated in the 1970s. *Agrobacterium* transfers DNA

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[2] The rates of mutagenicity vary greatly among plant species and conditions (Jiang et al., 2011; Stroud et al., 2013).

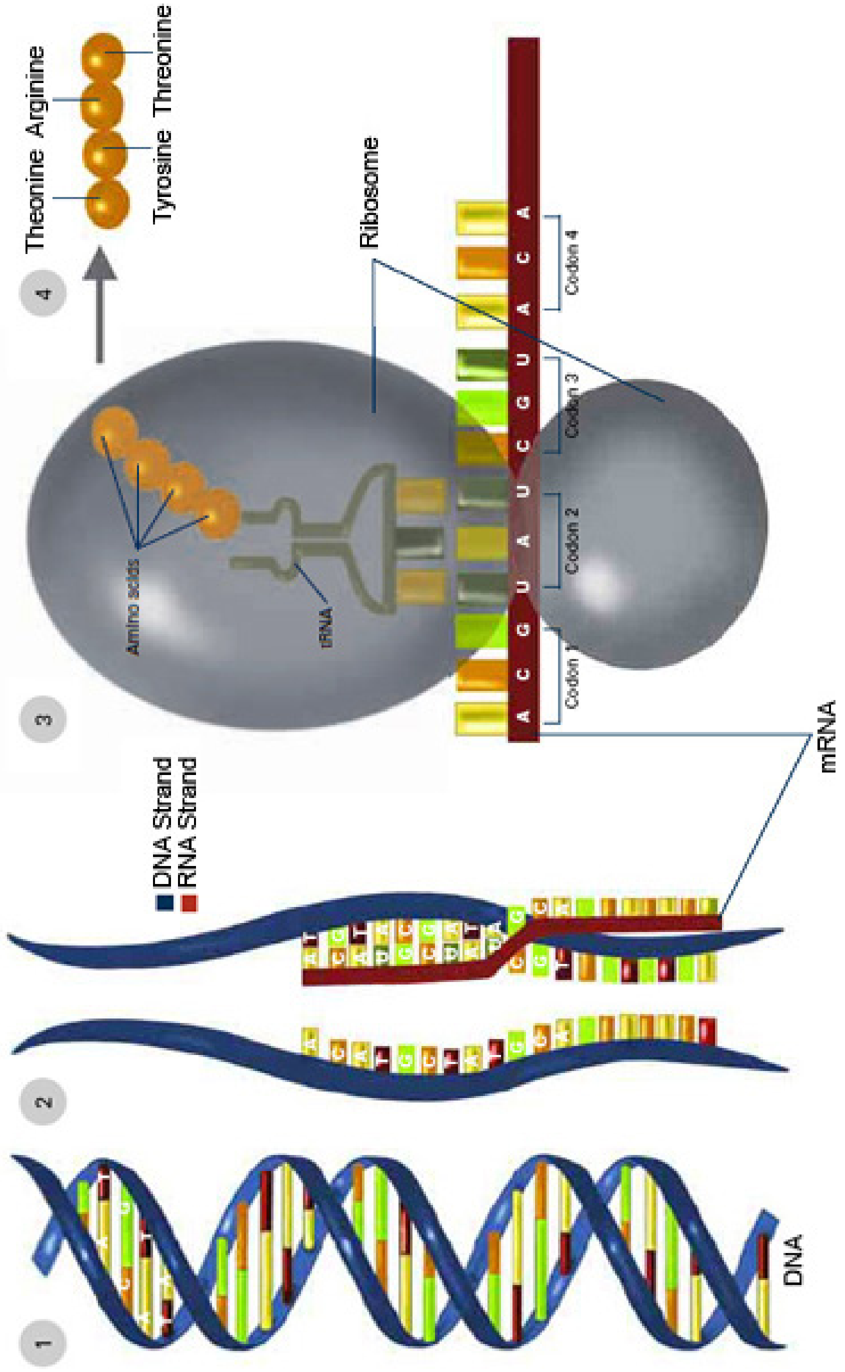
1
DNA
2
DNA Strand
RNA Strand
mRNA
3
A C G U A U C G U A C A
Codon 1
Codon 2
Codon 3
Codon 4
tRNA
Amino acids
Ribosome
4
Theonine
Arginine
Tyrosine
Threonine

FIGURE 3-3 Transcription of DNA into RNA, which is translated into proteins that collectively result in the expression of genetic traits.

SOURCE: National Institute of General Medical Sciences (2010).

NOTE: To express a genetic trait, information contained in DNA is copied (transcribed) into a molecule known as ribonucleic acid, or RNA. RNA specifies the synthesis of proteins. Thus, DNA carries the instructions for proteins, which are chainlike molecules (polymers) that are composed of sequences of amino acids. The genetic information is expressed when DNA (1) is transcribed to RNA (2). During transcription, a strand of DNA serves as a template for the formation of a complementary strand of messenger RNA (mRNA). Next, the messenger RNA moves from the cell nucleus to the cytoplasm, where ribosomes attach to the messenger RNA (3) and direct protein synthesis by reading the genetic code and building a chain of amino acids (4). The chain of amino acids forms a protein, which is responsible for or participates in the manifestation of one or more traits.

from a portion of a large tumor-inducing (Ti) plasmid into plant cells.[3] The portion of the Ti plasmid that is transferred is known as the transfer DNA (T-DNA), and it contains genes that—when expressed in plant cells—cause tumorous growth. It also contains genes that subvert plant metabolism to benefit the bacteria. By the late 1970s, pioneering scientists found that they could remove the genes normally transferred by *Agrobacterium* that cause crown gall disease and replace them with genes that they wished to insert into plants cells, thus establishing the bacterium as a useful vector for plant genetic engineering. Soon they were genetically engineering plants using *Agrobacterium*-mediated transformation of genes cloned into the T-DNA of the Ti plasmid.

In the early 1980s, it was clear that genetic engineering could have a considerable impact on plant agriculture. A reader perusing the expert scientific commentary and review papers of that time, typified by Barton and Brill (1983) and NRC (1984), would probably conclude that researchers had an extensive list of traits that might be endowed in crops by genetic engineering and were optimistic that crop improvements would ensue rapidly. Barton and Brill predicted that improvements could be made via genetic engineering to address insect control (with the use of *Bacillus thuringiensis* [*Bt*] genes), herbicide resistance for weed control, and resistance to drought and other stresses. The final sentence in their article sums up the optimism of the era: “The future of plant genetic engineering will be exciting, as much because of the applications we cannot yet predict as because of those already expected.”

Throughout the 1980s, academic laboratories and companies set out to produce plants that could be released as commercial products. The United States approved the first GE crops for release into the environment in 1985.[4] By 1988, the company Calgene had received approval from the U.S. government to field test what would eventually be known as the FLAVR SAVR™ tomato, a GE tomato that had a trait for delayed ripening. That tomato would later be the first GE crop grown for commercial sale after the 1994 growing season. In 1989, Monsanto Company received permits to field test soybean (*Glycine max*) that was resistant to the herbicide glyphosate and that was first sold commercially in the United States in 1996.[5]

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[3] A plasmid is a genetic structure in a bacterial cell that is physically separated from chromosomal DNA and can replicate independently.

[4] The first release-into-the-environment permit (found in the U.S. Department of Agriculture database hosted at www.isb.vt.edu) was granted to the company Agracetus and included GE maize, cotton, potato, soybean, tobacco, and tomato for a trait that was undisclosed because of confidential business information.

[5] Glyphosate is sold by Monsanto under the trademarked name Roundup. Soybean with the GE glyphosate-resistant trait sold by Monsanto is known as Roundup Ready soybean.

GE crop development from the 1980s to 2015 relied predominantly on the three key technologies discussed above: recombinant DNA, tissue culture, and *Agrobacterium*-mediated cell transformation. Another important tool, microprojectile bombardment, emerged in the latter half of the 1980s. Also known as biolistics or the gene-gun method, it was developed at least in part to increase the number of plant taxa that could be genetically engineered (Klein et al., 1987). The gene gun was invented by Sanford and colleagues at Cornell University. Various devices were engineered to accelerate micrometer-sized gold or tungsten particles, which were coated with DNA, to pierce plant cells for transformation. The biolistics device that was commercialized for plant transformation uses helium pressure to accelerate microprojectiles through a vacuum chamber to bombard plant tissue in Petri plates. Particle bombardment serves as a second reliable tool for genetic engineering, but many economically important crops that were thought to be nontransformable by *Agrobacterium*—such as maize—were later transformed routinely by using this bacterium (Gelvin, 2003). Almost all plant taxa (including ferns) have been shown to be amenable to *Agrobacterium*-mediated transformation (Muthukumar et al., 2013), although in some species only a few genotypes can be transformed efficiently.

GENETICALLY ENGINEERED CROPS IN THE EARLY 21ST CENTURY

Genetic engineering is a rapidly evolving technology. In 2015, *Agrobacterium*-mediated transformation described in the section above was being overtaken by new approaches (discussed in Chapter 7). This section reviews the crops and traits that had been developed and identifies where they were grown (if they were in commercial production) at the time this report was written.

Global Distribution of Genetically Engineered Crops

About 12 percent (179.7 million of 1.5 billion hectares) of global cropland produced GE crops in 2015 (FAO, 2015; James, 2015). Data for 2015 show that GE varieties were commercially available for nine food crops, three nonfood crops, and two types of flowers. GE maize and soybean were the most widely grown GE crops.

Production of GE maize has increased substantially since its first commercial release in 1996, when fewer than 300,000 hectares were planted (James, 1997). By 2006, 25.2 million hectares were in production worldwide, and the area more than doubled to 53.7 million hectares by 2015, representing one-third of all land planted to maize worldwide that year (James, 2006, 2015).

GE varieties dominated the soybean market in 2015; they were grown on about 80 percent of the 118 million hectares of soybean harvested in that year (James, 2015; USDA, 2016). As with maize, adoption of GE soybean varieties increased quickly after they were introduced in 1996. In 2001, 33 million hectares were grown globally (James, 2002); by 2015, over 92 million hectares were planted with GE varieties (James, 2015).

The seven other food crops of which GE varieties were grown in 2015 were apple (*Malus domestica*), canola (*Brassica napus*), sugar beet (*Beta vulgaris*), papaya (*Carica papaya*), potato, squash (*Cucurbita pepo*), and eggplant (*Solanum melongena*) (James, 2015). The contribution of GE varieties to the production of those crops was small, except for canola; GE varieties of canola constituted 24 percent of the 36 million hectares planted in 2015 (James, 2015).

With regard to crops that are mostly or entirely grown for nonfood uses, GE varieties of alfalfa (*Medicago sativa*), cotton (*Gossypium hirsutum*), and poplar (*Populus* spp.) were grown in 2015. Genetic engineering had also been used to change the color of carnations (*Dianthus caryophyllus*) and roses (*Rosa* spp.) that were sold commercially (S. Chandler, RMIT University, personal communication, December 7, 2015).

Production of GE crops in 2015 was distributed unevenly around the world (Figure 3-4). The United States produced 10 crops with GE varieties, followed by Canada with four. GE maize, soybean, and cotton were grown in many countries, whereas GE varieties of alfalfa, apple, poplar, potato, squash, and eggplant were grown in just one country each. Over 70 million of the 179.7 million hectares producing GE crops were in the United States.[6] GE crops produced in Brazil, Argentina, India, and Canada accounted for another 91.3 million hectares. The remaining 17.5 million hectares were spread among 23 countries.

In 2015, an alfalfa variety with reduced lignin was also being readied for the U.S. market, and Brazil had approved GE common bean (*Phaseolus vulgaris*) and GE eucalyptus (*Eucalyptus* spp.) for commercialization. GE varieties of rice, wheat, sorghum (*Sorghum bicolor*), and cassava (*Manihot esculenta*) were in various stages of development; the same was true for banana (*Musa* spp.), camelina (*Camelina sativa*), citrus (*Citrus* spp.), chickpea (*Cicer arietinum*), cowpea (*Vigna unguiculata*), groundnut (*Arachis hypogaea*), mustard (*Brassica* spp.), pigeon pea (*Cajanus cajan*), and safflower (*Carthamus tinctorius*) (James, 2014). A blight-resistant American chestnut (*Castanea dentata*) was also in progress. Many of those crops and traits are further discussed in Chapter 8.

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[6] Seventy million hectares is roughly half of all U.S. cropland. Thus, about 50 percent of cropland in the United States was producing GE crops when the committee was writing its report (Fernandez-Cornejo et al., 2014).

FIGURE 3-4 Location of commercially grown genetically engineered (GE) crops in 2015.
SOURCE: Adapted from James (2014, 2015).
NOTE: In addition to the crops depicted on the map, GE carnations (engineered for novel flower color) were grown in Colombia, Ecuador, and Australia and sold on wholesale cut flower markets in Canada, the United States, the European Union, Japan, Australia, Russia, and the United Arab Emirates (S. Chandler, RMIT University, personal communication, December 7, 2015; Florigene Flowers: Products. Available at http://www.florigene.com/product/. Accessed December 15, 2015). GE roses have been grown and commercially sold in Japan (S. Chandler, RMIT University, personal communication, December 7, 2015).

Genetically Engineered Traits in Commercially Produced Crops

As shown in Figure 3-4, 14 GE crops were in commercial production in 2015. However, GE crops can have one or more GE traits. For example, some varieties of soybean in the United States have been engineered to withstand one or more herbicides, whereas other varieties have been altered to produce more oleic oil (Table 3-1). GE maize varieties in the United States may be engineered to resist one or more herbicides and also contain several insecticidal proteins targeted at different species of insect pests (Box 3-1). Some maize varieties include a trait to enhance drought tolerance. Some crops are engineered to resist viruses, and others to delay ripening. Thus, describing a crop as "GE" is not informative about the purpose of the genetic alteration to the plant. This section reviews the commercialized GE traits in crops produced in 2015.

Herbicide Resistance

A herbicide-resistant (HR) trait allows a GE crop to survive application of a herbicide that would otherwise damage or kill a susceptible plant. In 2015, HR traits had been developed for nine different herbicides: eight HR traits for soybeans, six for cotton, five for maize, two for canola, two for sugar beet, and one for alfalfa (Table 3-1), but not all trait–crop combinations were in commercial production. For example, glufosinate-resistant sugar beet had been developed but was not commercially produced when the committee was writing its report. Some crop varieties that had stacked traits for resistance to two herbicides (for example, glyphosate and 2,4-D or glyphosate and dicamba) were in commercial development in 2015. However, in 1996–2015, most HR crops were engineered for resistance to only one herbicide, and the most common herbicide–HR crop combination used during that time was glyphosate with a glyphosate-resistant crop. First introduced in soybean in 1996, glyphosate resistance was also available in alfalfa, canola, cotton, maize, and sugar beet by 2015.

Insect Resistance

An insect-resistant (IR) trait incorporates insecticidal properties into a plant itself. A major example of GE insect resistance is the transfer of a gene coding for a crystalline (Cry) protein from the soil bacterium *Bt* to the plant (these Cry proteins are also called *Bt* toxins). The transferred protein is toxic to the target insect when the insect feeds on the plant. There are many kinds of Cry proteins that control various insect pests—primarily moths, beetles, and flies (Höfte and Whiteley, 1989)—and the different kinds can be stacked to protect a plant from more than one insect pest. At the time

TABLE 3-1 Genetically Engineered Traits Deregulated and Approved for Field Release in the United States as of 2015

Crop	Crop Scientific Name	Trait	Year Approved	Developer
Alfalfa	*Medicago sativa*	Glyphosate HR[a,b]	2005	Monsanto & Forage Genetics
		Reduced Lignin	2014	Monsanto & Forage Genetics
Apple	*Malus domestica*	Nonbrowning	2015	Okanagan Specialty Fruits
Canola	*Brassica napus/ Brassica rapa*	Oil Profile Altered[c]	1994	Calgene
		Glufosinate HR	1998	AgrEvo
		Glyphosate HR	1999	Monsanto
Cichory	*Cichorium intybus*	Male Sterility[c]	1997	Bejo
Cotton	*Gossypium hirsutum*	Bromoxynil HR[c]	1994	Calgene
		Bt IR[d]	1995	Monsanto
		Glyphosate HR	1995	Monsanto
		Sulfonylurea HR	1996	DuPont
		Glufosinate HR	2003	Aventis
		Dicamba HR	2015	Monsanto
		2,4-D HR	2015	Dow
Flax	*Linum usitatissimum*	Tolerant to Soil Residues of Sulfonylurea Herbicide[c]	1999	University of Saskatchewan
Maize	*Zea mays*	Glufosinate HR	1995	AgrEvo
		Bt IR	1995	Ciba Seeds
		Male Sterility[c]	1996	Plant Genetic Systems
		Glyphosate HR	1997	Monsanto
		Increased Lysine[c]	2006	Monsanto
		Imidazolinone HR[c]	2009	Pioneer
		Alpha-Amylase	2011	Syngenta
		Drought Tolerance	2011	Monsanto
		ACCase[e] HR	2014	Dow
		2,4-D HR	2014	Dow
		Increased Ear Biomass	2015	Monsanto
Papaya	*Carica papaya*	Ring Spot Virus VR[f]	1996	Cornell University, University of Hawaii, USDA Agricultural Research Service

continued

TABLE 3-1 Continued

Crop	Crop Scientific Name	Trait	Year Approved	Developer
Plum	*Prunus domestica*	Plum Pox VR[c]	2007	USDA Agricultural Research Service
Potato	*Solanum tuberosum*	*Bt* IR[c]	1995	Monsanto
		Potato Leafroll VR[c]	1998	Monsanto
		Potato Virus Y VR[c]	1999	Monsanto
		Low Acrylamide	2014	Simplot Plant Sciences
		Nonbrowning	2014	Simplot Plant Sciences
		Resistance to Late Blight Pathogen	2015	Simplot Plant Sciences
Rice	*Oryza sativa*	Glufosinate HR	1999	AgrEvo
Rose	*Rosa* spp.	Altered Flower Color	2011	Florigene
Squash	*Cucurbita pepo*	Zucchini Yellow VR	1994	Upjohn
		Watermelon Mosaic VR	1994	Upjohn
		Cucumber Mosaic VR	1996	Asgrow
Soybean	*Glycine max*	Glyphosate HR	1994	Monsanto
		Glufosinate HR	1996	AgrEvo
		High Oleic Oil	1997	DuPont
		Acetolactate Synthase HR[c]	2008	Pioneer
		Bt IR[c]	2011	Monsanto
		Improved Fatty Acid Profile[c]	2011	Monsanto
		Stearidonic Acid Produced[c]	2012	Monsanto
		Isoxaflutole HR[c]	2013	Bayer and M.S. Technologies
		Increased Yield[c]	2013	Monsanto
		Imidazolinone HR	2014	BASF
		2,4-D HR	2014	Dow
		HPPD[g] HR[c]	2014	Bayer/Syngenta
		Dicamba HR	2015	Monsanto
Sugar beet	*Beta vulgaris*	Glufosinate HR[c]	1998	AgrEvo
		Glyphosate HR	1998	Novartis & Monsanto
Tobacco	*Nicotiana tabacum*	Reduced nicotine[c]	2002	Vector

TABLE 3-1 Continued

Crop	Crop Scientific Name	Trait	Year Approved	Developer
Tomato	*Solanum lycopersicum*	Fruit Ripening Altered[c]	1992	Calgene
		Fruit Polygalacturonase Level Decreased[c]	1995	Zeneca & Petoseed
		Bt IR[c]	1998	Monsanto

NOTE: The table identifies the first time a trait was deregulated for a specific crop in the United States. Some deregulated trait–crop combinations have never been used in commercial production.

[a] HR = herbicide resistance.

[b] Returned to regulated status in 2007; returned to deregulated status in 2011.

[c] Trait–crop combination not in production in 2015.

[d] IR = insect resistance (different *Bacillus thuringienis* Cry genes inserted to encode proteins that kill specific species).

[e] Acetyl CoA Carboxylase inhibitor herbicide.

[f] VR = virus resistance.

[g] 4-Hydroxyphenylpyruvate dioxygenase inhibitor herbicide.

DATA SOURCE: USDA–APHIS Petitions for Determination of Nonregulated Status. Available at http://www.aphis.usda.gov/biotechnology/petitions_table_pending.shtml. Accessed December 20, 2015.

BOX 3-1
Stacked Traits

An organism can contain more than one GE trait. Introducing more than one GE trait is called stacking. The genetic material introduced comes from different sources or the GE traits differ or both. The GE traits can be in the same site in the genome or in different sites. Trait stacking does not include situations in which one of only two GE insertions into a plant consists of a selectable marker gene unless the marker gene affects the properties of the plant. Stacking of GE traits can be achieved either through genetic engineering or by conventional crossing of two plants, each of which has at least one GE trait.

of writing this report, *Bt* toxins were the only form of GE insect resistance that had been commercialized. In 2015, IR varieties of cotton, eggplant, maize, poplar, and soybean were in commercial production.

Virus Resistance

Virus resistance prevents a plant from being susceptible to specific viral diseases. In the virus-resistant (VR) crops engineered as of 2015, the coat-protein gene from the targeted virus (or viruses if protection from more than one is sought) is transferred into the crop. The transgene prevents the virus from replicating successfully in the host plant. Commercially grown VR varieties of papaya were developed by Cornell University, the University of Hawaii, and the Agricultural Research Service of the U.S. Department of Agriculture and were first introduced in the state of Hawaii in 1998. VR squash production began in the United States in the late 1990s. China approved commercial production of VR sweet pepper (*Capsicum annuum*) in 1998, but there was no commercial production of the crop at the time this report was written.

Other Traits in Commercial Production

HR, IR, and VR traits have been in continuous production since the late 1990s. Most of the GE crops in production in 2015 had resistance to one herbicide, contain one or more IR traits, or had both HR and IR traits. However, more GE traits are being introduced each year, and many are unrelated to prevention of damage from insects or to reducing competition with weeds.

In soybean, efforts have been made to increase oxidative stability of the oil to avoid trans-fats generated through the hydrogenation process and to enhance omega-3 fatty acid content of the oil for use in both food and feed. Oils with a high percentage of oleic acid (around 80 percent) require less processing and offer a route to decreasing the concentrations of trans-fats in food products. Genetic engineering has been used to create high-oleic acid soybean through gene silencing (Buhr et al., 2002). In 2015, high-oleic acid soybean was commercially available in North America and was produced on a small number of hectares in the United States for specialty-product contracts (C. Hazel, DuPont Pioneer, personal communication, December 14, 2015).

In maize, GE traits have been developed for drought tolerance and increased alpha-amylase content. The drought-tolerant maize variety developed by Monsanto, DroughtGard™, expresses a gene that encodes cold-shock protein B (cspB) from *Bacillus subtilis*; under some drought conditions, cspB expression results in higher yield than that of non-GE controls

(Castiglioni et al., 2008). By introducing the alpha-amylase enzyme into the maize endosperm through genetic engineering, the company Syngenta created a maize variety in which the grain is better suited as a feedstock for ethanol production than varieties that lack the enzyme.

In 2015, nonbrowning varieties of apple and potato were sold commercially. Genetic engineering was used to silence the expression of enzymes in the polyphenol oxidase family that cause browning of the crops' flesh after cuts or bruises. The nonbrowning trait was expected to reduce waste in apples and potatoes and to reduce the use of chemical antibrowning agents on cut apples. Six hectares of nonbrowning apple were planted in 2015, with an expected harvest date of September 2016 (N. Carter, Okanagan Specialty Fruits, personal communication, April 13, 2016).

In the GE nonbrowning potato, the gene that controls asparagine synthase production was also silenced to reduce the production of asparagine because, when potatoes are fried or baked at high temperature, asparagine breakdown results in the production of acrylamide, a potential carcinogen (Zyzak et al., 2003). Nine hundred thirty hectares of potato with GE traits for nonbrowning and low acrylamide were commercially grown in the United States in 2015 (C. Richael, Simplot Plant Sciences, personal communication, April 13, 2016).

Florigene, an Australian company, used genetic engineering to produce blue carnations and roses. The carnations are grown in Colombia, Ecuador, and Australia and shipped as cut flowers to Canada, the United States, the European Union, Japan, Australia, Russia, and the United Arab Emirates. GE roses have been grown and commercially sold in Japan (S. Chandler, RMIT University, personal communication, December 7, 2015).[7]

China has commercialized tomato with a GE trait for delayed ripening. However, that crop was not being produced when the committee was writing its report.

Genetically Engineered Traits Nearing Market Release

At the time of the report's writing, several GE traits aimed at crop quality were ready to begin commercial production. GE pest-resistant varieties for some crops that had not previously had GE traits were also in development.

Simplot Plant Sciences, the company that developed the potato with GE traits for nonbrowning and low acrylamide, was in the process of commercializing a second GE potato variety as this report was being written. The second variety was engineered to resist the pathogen responsible for

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[7] See also Florigene Flowers: Products. Available at http://www.florigene.com/product/. Accessed December 15, 2015.

late blight—the disease best known as a proximate cause of the Irish potato famine of the 1840s—in addition to the nonbrowning and low-asparagine traits.[8]

Brazil approved a variety of eucalyptus that was genetically engineered for higher yields in 2015. The yield enhancement was gained through the introduction of an endoglucanase gene from the small annual plant *Arabidopsis thaliana* (FuturaGene, 2015). Eucalyptus is grown primarily as a source of cellulose for such products as paper, and expression of the endoglucanase gene causes more cellulose to be deposited in cell walls.

Alfalfa engineered to contain lower concentrations of lignin in secondary cell walls, a trait that makes the alfalfa easier for cows to digest, was also near commercialization in late 2015. The reduction was achieved through the partial silencing of the gene that encodes an enzyme involved in the synthesis of the monolignol building blocks of lignin. The new GE trait will be available alone or as a stack with glyphosate resistance.

Pest resistance has been engineered into common bean and plum varieties. Brazil's government-owned research corporation, EMBRAPA, developed a GE virus-resistant bean (Faria et al., 2014) that attained approval for commercial production in 2014. Over the course of 24 years, a working group of European and U.S. scientists developed a plum (*Prunus domestica*) that was resistant to the plum pox virus (PPV), a serious pathogen that threatens stone fruits including plums, peaches (*Prunus persica*), and apricots (*Prunus armeniaca*) worldwide. Resistance to PPV uses co-suppression and RNA silencing (discussed more in Chapter 7). In 2015, PPV was not present in the United States, but the researchers had gained U.S. approval for the commercial production of GE plums, so they can be grown if the virus becomes a threat. Resistance had also been hybridized into many plum varieties grown in the United States to prevent plum production from being devastated if PPV emerges. VR plum has been field tested in Europe since the late 1990s. Scorza (2014) reported that European researchers were interested in submitting a request to the European Food Safety Authority for approval of GE plum because PPV is a major problem in Europe.

Genetically Engineered Traits or Crops That Have Been Discontinued or Were Never Commercialized

Many GE traits have been developed and never commercialized; others have been inserted into crops whose GE lines were never commercialized or were withdrawn from production after an initial period of commercialization. It is impossible to list every GE trait that has been developed because the traits become known only when a research entity brings a crop with a

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[8] More details on gene silencing and the GE potato are presented in Chapter 8.

GE trait to government regulatory authorities for approval. In this section, the committee reviews examples of GE traits and crops that were close to commercialization but were never sold or that were withdrawn from the market. Reasons have included business decisions based on nonprofitability or market failure, consumer nonpreference or social perceptions, and failure to comply with regulatory procedures.

The first commercial GE crop, the FLAVR SAVR tomato, which had delayed ripening that resulted in a longer shelf life, was originally intended for processing; however, having initially expressed interest, Campbell Soup Company decided not to use the GE tomato in its products after some members of the public expressed opposition (Vogt and Parish, 2001). The FLAVR SAVR tomato was instead planted for fresh market in 1994–1997 before being withdrawn from the market as unprofitable because it did not taste better and was more expensive than other tomatoes in the same market space (Bruening and Lyons, 2000; Martineau, 2001; Vogt and Parish, 2001).

Also in the mid-1990s, the company Zeneca marketed a GE tomato that had lower water content for use as tomato paste. The product was labeled as genetically modified. In 1996, the Safeway and Sainsbury grocery chains sold GE tomato paste under their labels in the United Kingdom. However, it was removed from the market in 1999 after sales declined following news-media reports of "biological effects . . . attributed to the process of genetic engineering" (Bruening and Lyons, 2000).

GE potatoes with IR and VR traits constitute an example of a GE crop that was withdrawn from commercial production because of governance decisions made by food retailers in the private sector and competition from other pest-control products. In 1995, Monsanto received U.S. government approval for a potato with the Cry3A (*Bt*) gene for the control of Colorado potato beetle (*Leptinotarsa decemlineata*), and 600 hectares of the IR potatoes were planted. GE potato resistant to potato leaf roll virus (*Polerovirus* spp.) was approved in 1998, and a variety resistant to potato virus Y was approved in 1999. The *Bt* trait was stacked with either the potato leaf roll virus trait or the potato virus Y trait. The area of GE potato production increased from 1995 to 1998 to about 20,000 hectares, or 3.5 percent of U.S. potato hectares (Hagedorn, 1999). However, the area planted declined sharply in 2000; the decline has been attributed to lack of acceptance by some consumers (Guenthner, 2002). In 2000, a large fast-food chain announced it would no longer purchase GE potatoes. The potato industry was not capable of segregating and testing to provide non-GE potatoes to customers (Thornton, 2003), and growers were concerned about growing a crop that their buyers would not purchase. In addition, many farmers adopted a newly introduced insecticide that controlled Colorado potato beetle and other pests rather than plant the GE variety (Nesbitt, 2005). In 2001, Monsanto closed its potato division.

Monsanto developed wheat that was resistant to glyphosate in the mid-1990s and had plans to commercialize it. However, because of lack of support from the wheat industry, the company did not take the GE wheat variety through the approval process necessary for commercialization (Stokstad, 2004). Some growers were concerned that GE wheat would be rejected by foreign markets.

The company ProdiGene was interested in using genetic engineering to produce pharmaceutical or industrial products in GE plant systems. However, it failed to comply with U.S. regulatory procedures. Not only did its product never come to market, but the company was fined for its violations (Box 3-2).

BOX 3-2
The ProdiGene Incident: Noncompliance with Regulatory Processes

The production of plant-based pharmaceutical or industrial proteins has two main components: the GE crop and the bioprocess to achieve the final product. ProdiGene was a private biotechnology company based in College Station, Texas, that focused on the use of GE plants to produce proteins, enzymes, and molecules for pharmaceutical and industrial applications. In 1997, ProdiGene began field trials for GE maize plants in Nebraska, Texas, and Iowa. The company's largest trial was conducted in 2001 to produce a combination of proteins in about 22 hectares of maize.[a]

In mid-2002, the company entered into an agreement with Sigma-Aldrich Fine Chemicals to manufacture recombinant trypsin using ProdiGene's GE plant system. The GE maize expressed trypsin genes from domestic cow in the grain (USDA–APHIS, 2004). The process promised to be scalable and profitable for both sides because of a high demand for animal-free products; traditional commercial production of trypsin involves animal systems (Wood, 2002). However, during field trials of commercial production of recombinant proteins in GE maize, the company was faced with a series of noncompliance events that led to punitive action.

In September 2002, inspectors from the U.S. Department of Agriculture (USDA) found volunteer[b] maize growing in an Iowa soybean field that had been a field-test site for ProdiGene's GE maize during the previous growing season. ProdiGene failed to notify USDA, in accordance with permit conditions, about volunteer maize plants with tassels within 24 hours of their discovery. After the discovery by the inspectors, ProdiGene destroyed some 61 hectares of maize seed and plant material within 400 meters of the previous year's test plot under the inspectors' supervision.

In October 2002, USDA inspectors again found volunteer GE maize with tassels from the previous year's Nebraska test sites growing in a soybean field. The

Lysine is the limiting essential amino acid in most cereal-based diets, so high lysine in maize is a trait of interest. Maize-based diets are particularly deficient in lysine because the storage protein in maize, zein, is very low in lysine. Expression of a bacterial feedback-insensitive enzyme (dihydrodipicolinate synthase) that increases lysine synthesis was used to make a GE high-lysine maize (Lucas et al., 2007), but Monsanto decided not to commercialize the product.

The evolving story of *Bt* eggplant in India, Bangladesh, and the Philippines illustrates complex interplays of social and legal aspects that could lead to different outcomes among these countries, all of which had previously agreed that *Bt* eggplant was a high-priority product for them

company was ordered to remove all the volunteer maize to prevent its harvesting with the soybeans. However, the company failed to remove the volunteer maize, and about 500 bushels of soybean were harvested and sent to a grain elevator, where they were mixed with another 500,000 bushels of soybean. At that point, all soybean movement at the elevator was stopped, and USDA destroyed all the soybeans.

After an investigation by USDA's Investigative and Enforcement Services and a formal administrative proceeding, ProdiGene was issued a $250,000 penalty. In an additional consent decision, ProdiGene agreed to reimburse USDA for the cost of buying, moving, and incinerating the soybeans and to post a $1 million bond to demonstrate financial responsibility for any future violations. USDA provided an interest-free loan to ProdiGene for the full $3.75 million penalty and clean-up cost. When International Oilseed Distributors, Inc. bought ProdiGene in August 2003, it assumed the unpaid portions of the USDA loan.

In 2004, a USDA inspector found volunteer maize in baled oats that had been grown in the fallow zone alongside a ProdiGene test field that contained a maize variety engineered to produce pharmaceutical or industrial compounds. The baled oats were to be used as on-farm animal feed. The inspector found volunteer maize growing and flowering in the fallow zone surrounding the test field and in a nearby sorghum (*Sorghum bicolor*) field planted within a 1.6-km isolation distance. As part of its remedial action, ProdiGene destroyed all volunteer maize in the isolation zone and plowed under the sorghum field under USDA supervision; all suspect oat bales were quarantined and later destroyed.

In a July 26, 2007, settlement with USDA, ProdiGene, Inc. paid a $3,500 civil penalty and agreed that neither it nor "its successors in interest" would ever again apply to USDA for a notification or permit to introduce GE products.

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[a] Information Systems for Biotechnology. Available at http://www.isb.vt.edu/search-release-data.aspx. Accessed September 25, 2015.

[b] A *volunteer* is a plant that was planted in the previous season but that sprouts and grows in the next season. It is particularly noticeable when the field has changed crops between seasons, such as from maize to soybean.

(Box 3-3). The case of glyphosate-resistant alfalfa, which was on the market in 2015, demonstrates the influence of legal actions on the commercial status of GE crops in the United States (Box 3-4).

EVOLUTION OF REGULATORY POLICIES FOR GENETICALLY ENGINEERED CROPS AND FOODS

The section "Governance of Genetically Engineered Crops" in Chapter 2 and the section above contain many references to regulatory oversight

BOX 3-3
The Unfolding Story of *Bt* Eggplant in Bangladesh, India, and the Philippines

Eggplant is an economically and nutritionally important crop in South Asia and Southeast Asia, where it is widely cultivated and consumed. Eggplant is susceptible to the eggplant fruit and shoot borer (*Leucinodes orbonalis*; EFSB). A priority-setting exercise conducted in India, Bangladesh, and the Philippines with local stakeholders in the public and private sectors identified *Bt* eggplant with resistance to EFSB as a high-priority product (Gregory et al., 2008). Varieties of *Bt* eggplant were later produced through a public–private partnership that included several different entities and were submitted for regulatory approval in the three countries. At the time of writing this report, commercial release had taken place in Bangladesh but not in India or the Philippines. Approval of *Bt* eggplant was pending in India in 2009 but was halted in early 2010 when the minister of environment and forests responded to allegations by some members of the public that there was insufficient data to confirm that the crop was safe to eat. The minister declared a moratorium on the commercial release of *Bt* eggplant (Jayaraman, 2010). Field trials were reinitiated in 2014 under the impetus of a new Indian government, but according to local media reporting, Greenpeace and others filed a plea to the Indian Supreme Court for the trials to be banned (Chauhan, 2014). *Bt* eggplant trials were going on in the Philippines in September 2013, when a Philippine court ordered that they be stopped because of concerns that GE crops posed risks to human health and the environment after a campaign led by Greenpeace (Laursen, 2013). In April 2014, a group of farmers asked the Philippine Supreme Court to reverse the ruling; in September 2014, the Supreme Court allowed the Biotechnology Coalition of the Philippines to become involved in the case. The Supreme Court affirmed the lower court's ruling to permanently ban field trials for *Bt* eggplant on December 8, 2015 (InterAksyon.com, 2015). In October 2013, after 7 years of field and greenhouse trials, Bangladesh approved the release of *Bt* eggplant for seed production and commercialization; planting started in early 2014 (the wet season) (Choudhary et al., 2014). In the wet and dry seasons of 2014, 12 hectares total of *Bt* eggplant were planted in Bangladesh (James, 2014). In 2015, 25 hectares were planted (James, 2015).

BOX 3-4
The On, Off, and On Again Case of Genetically Engineered Alfalfa

The experience of glyphosate-resistant alfalfa in the United States is an interesting example of the capacity for fluidity in the commercial status of GE crops. Glyphosate-resistant alfalfa was planted commercially in June 2005 after USDA completed an environmental assessment (EA) with a finding of no significant impact on the environment (USDA–APHIS, 2005). In 2006, a lawsuit was filed by the Center for Food Safety and others in the U.S. district court for the northern district of California on the basis that USDA had not completed an environmental impact statement (EIS). The plaintiffs claimed that there would be adverse effects on farmers who wished to grow non-GE alfalfa due to gene flow (and thus loss of seed purity), increased evolution of glyphosate-resistant weeds, and increased glyphosate use. In February 2007, the judge ruled that the EA was inadequate and ordered USDA to prepare an EIS (*Geertson Farms v. Johanns*, 2007). The 80,000 hectares of glyphosate-resistant alfalfa already planted along with fields planted by March 30, 2007, were allowed to remain in production. The crop could be harvested and sold, but the court ordered that stewardship plans be followed to ensure that cross-contamination with non-GE alfalfa would be minimized. However, no seed of glyphosate-resistant alfalfa could be sold after March 12, 2007. On March 23, 2007, USDA published a notice of the return of glyphosate-resistant alfalfa to regulated status (USDA–APHIS, 2007). USDA completed the EIS in 2010 and returned glyphosate-resistant alfalfa to deregulated status in January 2011; this meant that it could again be sold commercially (USDA–APHIS, 2011).

or approval granted by governments for GE crops and food derived from GE crops. Why did governments decide to regulate these products and how are regulations structured? In the section below, the committee provides a brief history of why government regulations emerged for GE crops and the different ways in which governments have approached regulation of GE crops.

Policy Responses Due to Scientific and Public Concerns

As alluded to in Chapter 1, concerns about potential biosafety risks posed by genetic engineering surfaced in the scientific community almost immediately after the publication of the Cohen et al. (1973) article that described rDNA technology. Scientists attending the Gordon Conference on Nucleic Acids in 1973 called for the National Academy of Sciences to convene a study panel to develop guidelines for safe research on recombinant molecules (Singer and Soll, 1973). The 1974 report issued by the Committee on Recombinant DNA Molecules recommended that scientists voluntarily defer conducting higher-risk research in view of the uncertainties about potential biosafety risks, pending the development of biosafety guidelines (Berg et al., 1974). That committee was concerned particularly about the potential for rDNA-modified *Escherichia coli* bacteria to be accidentally disseminated to laboratory workers or the broader human, animal, plant, and bacterial populations with "unpredictable effects." The report also recommended that the National Institutes of Health (NIH) establish an advisory committee on biosafety guidelines for rDNA research and called for an international scientific conference to address the "appropriate ways to deal with the potential biohazards of recombinant DNA molecules" (Berg et al., 1974). The International Conference on Recombinant DNA Molecules was convened in February 1975 at the Asilomar Conference Center in California. The attendees developed biosafety principles that provided guidance for safe research practices with rDNA molecules in light of risks posed by the research and that allowed for the end of the voluntary research moratorium (Berg et al., 1975).

NIH was also responsive to the earlier recommendations and established the Recombinant DNA Molecular Advisory Committee (later renamed the Recombinant DNA Advisory Committee) in October 1974. Immediately after the Asilomar conference, the NIH advisory committee met to develop research guidelines, which were issued in June 1976 as *Guidelines for Research Involving Recombinant DNA Molecules* (NIH, 1976). The early NIH guidelines succeeded in allowing laboratory research on rDNA molecules to proceed safely. The guidelines have been modified numerous times but remain in effect as of May 2016 and focus on physical and biological containment for research based on the perceived biosafety or environmental risks of the research.

However, as research continued in the 1970s and 1980s, a number of scientists and civil society groups concerned about the potential biosafety risks associated with rDNA and about broader social and ethical issues regarding the application of the technology began to publicize their criticisms and organize opposition in the United States. As chronicled by Schurman and Munro (2010), concerns initially gained traction in a loose network of critics, including consumer, environmental, and social-justice organizations as well as groups involved in international development projects and large-scale industrialized agriculture.

Several events in the 1980s led to broader and more organized opposition. In 1980, the U.S. Supreme Court decided the case of *Diamond v. Chakrabarty*, upholding the patentability of living, human-made organisms. The ruling fueled concerns about the ethical implications of patenting life and the privatization of germplasm in seeds that had been traditionally viewed as a "commons" shared by all (Jasanoff, 2005). In 1983, NIH approved the first environmental release of a GE bacterium, which had been engineered to increase the resistance of crops to frost. The decision sparked opposition from environmental and other citizen groups and generated news-media attention. Concerned groups successfully challenged NIH's approval (*Foundation on Economic Trends v. Heckler*, 1985). In the mid-1980s, the development of a synthetic version of bovine somatotropin derived from GE bacteria, to be administered to cows to increase milk production, also generated opposition from a diverse coalition, including small dairy farmers and animal-welfare groups.

As time went by, European civil society groups—including farmer organizations and groups concerned with food safety, animal welfare, and the environment—amplified concerns about genetic engineering in agriculture (Schurman and Munro, 2010). Public concerns about the safety of the food supply were heightened in Europe by a series of food scares in the mid-1990s, including a major outbreak of mad cow disease.

In response to the uncertainty about how this new technology would function in the environment and to public concerns, some governments developed regulatory approaches to GE crops and to food derived from GE crops. Governments adopted different regulatory responses that depended in part on public opinion and on support and opposition by important constituencies.

Different Policy Approaches to Genetically Engineered Crops and Food

The differences in regulatory approaches among countries are discussed in Chapter 9. This section notes some salient points to provide context for later chapters.

Governmental regulatory approaches of GE crops vary in several key dimensions, including the scope of products subject to the regulatory schemes. Countries have differing statutory frameworks for making decisions that reflect the cultural traditions and risk tolerances of their citizens. Decision-makers consider input from diverse groups, which may include environmental and food-safety organizations, organic-crop farmers, large-scale farmers, animal producers, consumers, multinational agricultural companies, and many entities that are involved in the complex global food-production and food-distribution chain. As a result, it is not surprising that countries' regulatory policy choices reflect different policy tradeoffs. (Chapter 9 provides a more detailed comparison of the regulatory systems of the United States, Canada, Brazil and the European Union.)

The scope of regulations differs among countries. Some decide the regulatory status of each product based on the process used to develop the product, that is, the regulations apply to crops made with genetic-engineering techniques but not to crops bred or produced by conventional breeding. Others focus on the potential risks associated with final products, not the process by which they are made.

Regulatory schemes also differ among countries in how the responsibilities for risk assessment and risk management are allocated. In some countries, the same agency is responsible both for conducting the risk assessment of a regulated product and for making the final approval decision on the basis of meeting a safety standard. The U.S. regulatory system is organized along those lines (Box 3-5). Other governments have separated risk assessment, which is the task of a scientific or technical body, from the final approval decision, which is given to a different government agency that can consider issues that go beyond safety concerns.

BOX 3-5
U.S. Regulatory Framework for Genetically Engineered Crops

The Coordinated Framework for the Regulation of Biotechnology was established in 1986 and describes the U.S. regulatory policy for ensuring the safety of biotechnology products, including field trials and cultivation of GE crops and safety reviews of foods derived from them (OSTP, 1986). Three regulatory agencies have jurisdiction over different aspects of GE crops (Figure 3-5):

- USDA's Animal and Plant Health Inspection Service (APHIS) regulates GE plants to control and prevent the spread of plant pests that could damage crops, plants, or trees.
- The U.S. Environmental Protection Agency (EPA) regulates the safety of pesticides and "plant-incorporated protectants" for the environment and human health.
- The U.S. Food and Drug Administration (FDA) oversees the safety of food and feed, including the review of data used to compare GE food with its conventional counterpart (FDA, 1992).

The Coordinated Framework has been regularly updated since 1986, and a revision was initiated in July 2015 to modernize the regulatory system, including to "promote public confidence in the oversight of the products of biotechnology through clear and transparent public engagement" (OSTP, 2015).

Regulatory approaches can affect how quickly GE crops are adopted by growers in different countries. Some countries adopted regulatory policies that allowed relatively quick approval of new GE crop varieties; others adopted a more cautious regulatory stance and approved relatively few new GE foods and crops. Some countries adopted regulatory systems fairly quickly; others still have not, which effectively has resulted in a ban on the import or cultivation of GE foods and crops. One author categorized first-generation regulatory systems for GE crops into four models according to their overall orientation to biotechnology (Paarlberg, 2000). Frameworks

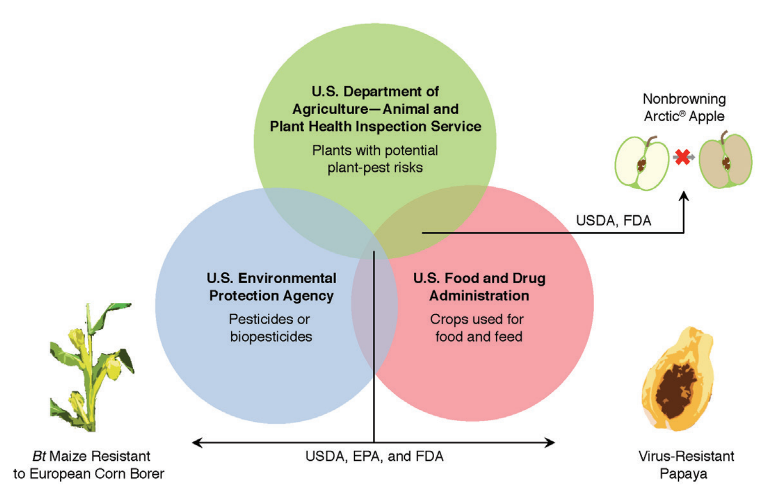

FIGURE 3-5 U.S. regulatory agencies that have responsibility for genetically engineered (GE) crops.
SOURCE: Based on Turner (2014).
NOTE: Depending on the GE trait in question, evaluation by one or all three of the agencies within the Coordinated Framework may be required before commercial release of a GE crop. For example, GE virus-resistant papaya went through the regulatory process of all three agencies. The use of *Agrobacterium tumefaciens* to transfer virus resistance was classified as use of a plant pest by APHIS, EPA classified virus resistance as conferring pesticidal quality, and consultation was completed with FDA because the papaya was intended for human consumption. In contrast, GE nonbrowning apple required evaluation by only two agencies because *A. tumefaciens* was used (APHIS) and food-safety assessments were required (FDA). Evaluation by EPA was not required because the gene responsible for the nonbrowning trait was not classified as a plant-incorporated protectant.

that encouraged the development of GE crops were deemed *promotional*; policies that were neutral—neither encouraging nor discouraging GE crops—were termed *permissive*; *precautionary* policies tended to slow the adoption of GE crops and foods; and *preventive* policies were intended to block the technology. Precautionary policies are discussed further in Chapter 9 (see Box 9-2).

CONCLUSIONS

The introgression of GE traits into crops was preceded by millennia of trait introductions into domesticated crops through selection and by rapid advances in plant breeding in the 20th century. The deciphering of the genetic code in the mid-20th century, plant-breeding tools (including tissue culture), and the discovery of the properties of *Agrobacterium tumefaciens* made recombinant-DNA technology in plants possible. GE traits were present in 14 crops in 2015. GE varieties dominated the planted area of soybean and cotton and were planted on one-third of maize hectares and one-fourth of canola hectares in the world in 2015. However, GE varieties had not been developed for most crops, and GE crops were grown on 12 percent of the world's cropland.

Several GE traits had been developed, but few of these were available in commercial crop varieties in 2015. Most commercially available traits in the first 20 years of GE crops were aimed at providing herbicide resistance to the crop or protecting the crop from insect damage. A few crops that had been genetically engineered to be resistant to viruses or to not turn brown when cut were also commercially available. Other types of traits, such as those conferring improved nutritional qualities or better composition for ethanol feedstock, were in commercial production, and a wider variety of traits were being readied for market release.

Approval by regulatory agencies clearly is instrumental in a GE crop's ability to enter the marketplace. The regulatory systems of some governments are more encouraging to GE-crop commercialization than others. Regulatory systems reflect different cultural traditions, histories, and risk tolerances in the constituencies of each country.

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4

Agronomic and Environmental Effects of Genetically Engineered Crops

This chapter examines the evidence on agronomic and environmental effects of currently commercialized genetically engineered (GE) crops. The analysis in this chapter is retrospective, looking at the effects that have occurred between the 1990s, when GE crops were first commercialized, and 2015. Although this chapter mentions general economic effects in a few places, full discussion of this topic is in Chapter 6.

As stated in Chapter 3, the United States was the first country to commercialize GE crops. Roughly half of U.S. land in crop production in 2014 was planted with GE crops—primarily maize (*Zea mays*), soybean (*Glycine max*), and cotton (*Gossypium hirsutum*)—and this area made up 40 percent of the world's production of GE crops (Fernandez-Cornejo et al., 2014; James, 2015). Given its market share, it is not surprising that much of the research on agronomic and environmental effects of genetic engineering in agriculture has been conducted in the United States. The committee relied primarily on that literature for much of its analysis, but it also drew on studies available from other countries that produce GE crops. Chapter 3 noted that most GE crops in production from the 1990s to 2015 were engineered with resistance to herbicides, resistance to insects, or a combination of the two; this review of agronomic and environmental effects therefore is focused on these traits.[1]

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[1] The committee recognizes that there are other approaches to managing crop pests besides GE crops; many of these, including the implementation of production systems the use agroecological principles to reduce the need for pesticides, were addressed in the 2010 National Research Council report *Toward Sustainable Agricultural Systems in the 21st Century* (NRC, 2010b). The present committee is aware of the central role that agroecology plays in fostering resilience in agriculture, but its report focuses specifically on the role and effects of GE crops.

The chapter begins with an analysis of the interaction between genetic-engineering technology and crop yield. That is followed by an examination of the agronomic effects of insect-resistant (IR) crops, specifically in terms of crop yield, insecticide use, secondary insect-pest populations, and the evolution of resistance to the GE trait in targeted insect populations. A similar review is conducted for the effects related to herbicide-resistant (HR) crops. There is discussion of the effects on crop yield of herbicide and insect resistance used together. Then the chapter turns to the environmental effects of IR and HR crops on the farm and beyond, including effects on biodiversity in plant and animal communities and diversity of crop species and varieties[2] planted on farms and potential effects of GE crops on landscapes and ecosystems. A GE variety's characteristics are due to a combination of the GE trait and the background germplasm into which the trait is placed. Therefore, the committee has endeavored to be specific about the effect of the trait itself on the crop's performance and environmental effects. Unless otherwise noted, whenever a difference is noted in this chapter it is statistically significant.

EFFECTS OF GENETIC ENGINEERING ON CROP YIELDS

Over the course of the study, the committee heard from speakers and received public comments that indicated that GE crops and their accompanying technologies were not substantially increasing crop yields; other comments and speakers endorsed genetic engineering as a contributor to yield increase, yield stabilization, or both.[3] Before examining the evidence available on the effects on crop yields, it is useful to understand the factors that influence crop yield in general.

Potential versus Actual Yield

The distinction between potential yield and actual yield has been discussed in an earlier National Research Council report (NRC, 2010a)[4] and other studies and reports (Sinclair, 1994; van Ittersum and Rabbinge, 1997; Gurian-Sherman, 2009; Lobell et al., 2009). Potential yield is the theoretical yield a crop genotype can achieve without any limitations of water or

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[2] The term *variety* is used throughout this chapter in its most general sense to encompass varieties, cultivars, and hybrids.

[3] Some of the comments expressing these views can be found in Appendix F.

[4] In the 2010 National Research Council report, potential yield was defined as "the yield that would be realized in the absence of damage caused by pests (i.e., weeds, insects)" (NRC, 2010a:138). That report acknowledged that such weather conditions as wind, rain, drought, and frost could affect yield. In the present report, the definition of potential yield includes more detail to capture those limiting factors.

nutrients and without losses to pests and disease (van Ittersum et al., 2013), given a specified carbon-dioxide concentration, temperature, and incident photosynthetically active radiation (Figure 4-1). Limitations of natural nutrient and water availability cause gaps between the potential yield and actual yield if nutrient and water supplementation are not possible. Actual yield may be further curtailed by "reducing factors," which can be organized into three main groups:

- Insect pest and diseases, which physically damage crops.
- Weeds, which reduce crop growth by competition for water, light, and nutrients.
- Toxicities caused by waterlogging, soil acidity, or soil contamination.

Genetic improvement of crops can close the gap between actual yield and potential yield or it can increase the overall potential yield. Such change can be accomplished in three ways. First, the potential yield can be increased; for example, the canopy architecture of the plant can be improved

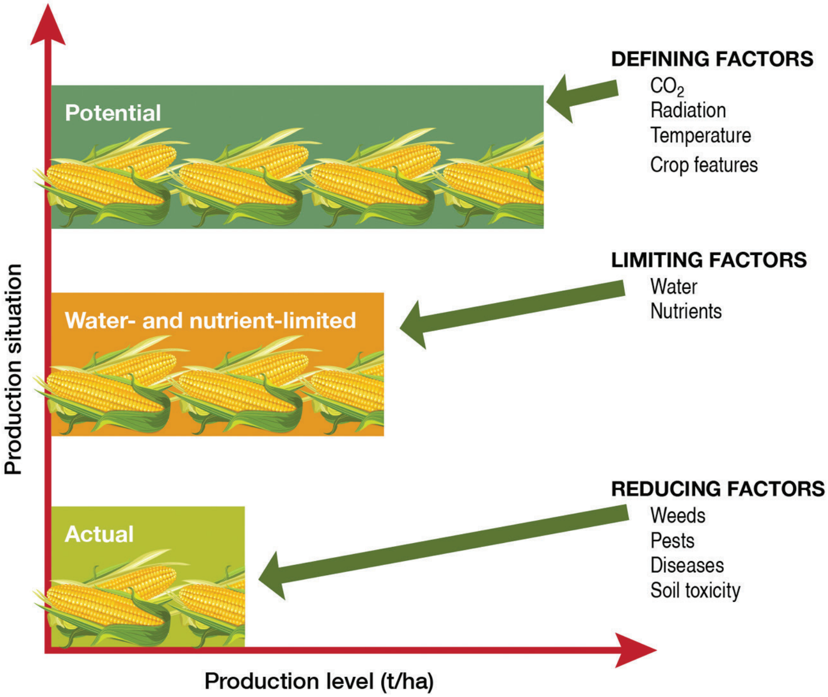

FIGURE 4-1 Factors that determine crop yield.
SOURCE: Based on van Ittersum et al. (2013).

to increase the conversion of photosynthetically active radiation through photosynthesis. Second, limitations of water and nutrient availability can be ameliorated by enhancing the efficiency with which water and nutrients are captured and used for crop growth. Third, factors that reduce yield can be mitigated by protecting the crop from pests, including weeds, insects, and disease.

In general, all three kinds of improvement can be accomplished through conventional plant breeding (described in Chapters 2 and 3), genetic engineering, or a combination of the two. For example, conventional plant breeding in the 1960s and 1970s led to the development of semi-dwarf wheat (*Triticum aestivum*) and rice (*Oryza sativa*), which had greater potential yields than earlier varieties. Selection and mutagenesis, both conventional plant-breeding techniques, were used to develop varieties of maize, canola (*Brassica napus*), rice, wheat, and sunflower (*Helianthus annuus*) that were resistant to imidazolinone herbicides (Tan et al., 2005), thereby reducing competition between crops and weeds for water, light, and nutrients when the herbicide was applied.

As of 2015, most GE crops contained traits that were intended to reduce crop competition with weeds, prevent damage from insects, or both. A few commercialized crops were engineered for protection against viruses and others for environmental (abiotic) stress resistance, but little information was available on the effects of these GE traits on yield (Box 4-1). A 2010 National Research Council report on the impacts of GE crops, which focused on the United States, concluded that "GE traits for pest management have an indirect effect on yield by reducing or facilitating the reduction of crop losses" (NRC, 2010a:138). That is, GE traits for herbicide, insect, and virus resistance have the potential to close yield gaps, but they do not increase the potential yield of a crop. That report found that the yields of HR crops had not increased because of the HR trait and that the yields of IR crops had increased in areas that suffered substantial damage from insects that were susceptible to *Bt* toxins. That report also concluded that effects of GE crops change with time.

Few crops that target the yield-limiting factors of nutrient and water availability have been commercialized. A variety of maize with drought tolerance was commercially available when the committee was writing its report. Chang et al. (2014) evaluated the potential for eight drought-tolerant GE maize hybrids to increase grain production in high-water-deficit environments in South Dakota in 2009 and 2010. They found that the trait did not significantly affect yield components, distribution of above-ground to below-ground biomass, or grain yield. Drought-tolerant maize is discussed further in Chapter 8.

The committee could only find one example of yield enhancement, that is, an increase in potential yield through genetic engineering. It in-

BOX 4-1
Yield Effects in Virus-Resistant Crops

Only a few crops have genetically engineered virus-resistant (VR) traits, and they are not planted on many hectares or widely studied. However, VR papaya and VR squash are grown commercially, and the committee reviewed the available literature to assess the effects of the VR trait on crop yield. In theory, if the resistance trait is successful, it should protect yield when the crop is exposed to the relevant pathogen.

Papaya ringspot virus arrived in Hawaii's main papaya production region in 1992 (Manshardt, 2012). In 1992, papaya production in the state was 33,065 kilograms/hectare (HASS, 1993); in 1998, it was 21,072 kilograms/hectare (HASS, 2000). Ferreira et al. (2002) reported that fruit production in field trials of VR papaya planted in 1995 was 3 times greater than the average production in 1988–1992, before the papaya ringspot virus affected Hawaiian papaya production. VR papaya was introduced in 1998; as of 2009, it accounted for over 75 percent of papaya hectares in Hawaii (USDA–NASS, 2009).

The committee could not find recent research on VR squash. The most current source of information available was Fuchs and Gonsalves (2008), which reported that VR squash accounted for 12 percent of U.S. squash production and was grown in New Jersey, Florida, Georgia, South Carolina, and Tennessee.

volved a single-gene approach; a reported 20-percent increase in biomass yield of eucalyptus (*Eucalyptus* spp.) trees resulted from the expression of an endoglucanase gene from the small annual plant *Arabidopsis thaliana* (FuturaGene, 2015). Eucalyptus is grown primarily as a source of cellulose for such products as paper, and expression of the endoglucanase gene causes more cellulose to be deposited in cell walls of the transgenic plants. Transgenic eucalyptus that expresses endoglucanase was approved for cultivation on tree plantations in Brazil in 2015.

Effects of Genetically Engineered Traits versus Conventional Plant Breeding on Yield

The committee heard concerns from the public and from researchers that GE crops commercialized up to 2015 had not contributed to an increase in yield as much or as effectively as conventional plant breeding had (Cotter, 2014; Goodman, 2014; Gurian-Sherman, 2014; Dever, 2015). It has often been difficult to separate the effects of GE traits and conventional breeding on yield over the last two decades because genetic engineering and conventional breeding have been used together in bringing GE traits into commercialization. If more effort is given to the conventional breeding of varieties with specific GE traits than of those without them, the greater yield of the GE varieties could be due largely to the conventional-breeding component.

The committee examined data on farm yields of the major crops in the United States that have been engineered since the 1990s in a general attempt to determine whether there is an obvious signature of the genetic-engineering era. In Figure 4-2, Duke (2015) showed the changes in yield of soybean, maize, and cotton in the United States from 1980 to 2011 on the basis of data from National Agricultural Statistics Service (NASS) of the U.S. Department of Agriculture (USDA) and provided a best-fit linear-regression line through the data points. Yield of all three crops has increased dramatically since 1980. If there was a change in the slope of increase in yield since the commercialization of GE varieties (marked by the dashed line), it could be taken as circumstantial evidence but not proof that genetic engineering caused a more rapid increase in yields. However, there is no obvious change in the slope for cotton and maize, which have the *Bt* and HR traits, or for soybean, which has only the HR trait. One could move beyond the rules of parsimony and hypothesize that, without the introduction of GE traits, the rate of yield increase would have declined. Mechanisms that could support such a hypothesis include a recent decline in conventional-breeding effort, diminution in genetic variation available to conventional breeders, and adverse effects of global climate change. The committee found no evidence of such mechanisms.

From the same data on maize yield used by Duke (2015), Leibman et al. (2014) argued that the slope of increase in yield has increased since commercialization of GE traits (Figure 4-3), although no statistical-significance value is provided for this change in slope. Leibman et al. speculated on how the more rapid change in yield improvement could change yields in the future. If such a change is significant, it will be important to determine whether it is the result of farming practices, GE traits, increased efforts in conventional breeding or emerging genetic-engineering technologies (see Chapter 7), or some combination thereof. Whatever the causes, yields have been increasing since the commercialization of GE traits, and there is no obvious sign of an increase in the relative variance in yield among years.

FINDING: The nation-wide data on maize, cotton, or soybean in the United States do not show a significant signature of genetic-engineering technology on the rate of yield increase. This does not mean that such increases will not be realized in the future or that current GE traits are not beneficial to farmers.

RECOMMENDATION: 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.

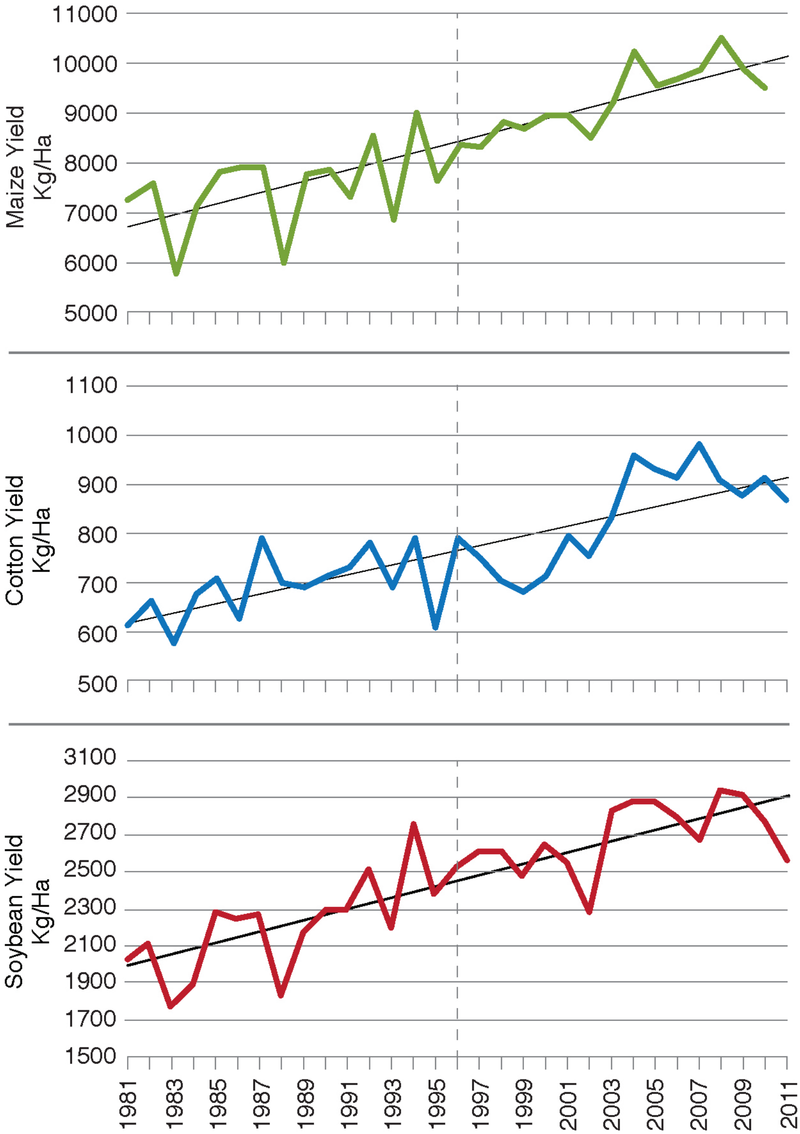

FIGURE 4-2 Yields of maize, cotton, and soybean in the United States, 1980–2011.
SOURCE: Duke (2015).
NOTE: Dashed line indicates when genetically engineered varieties of these crops were first introduced in the United States.

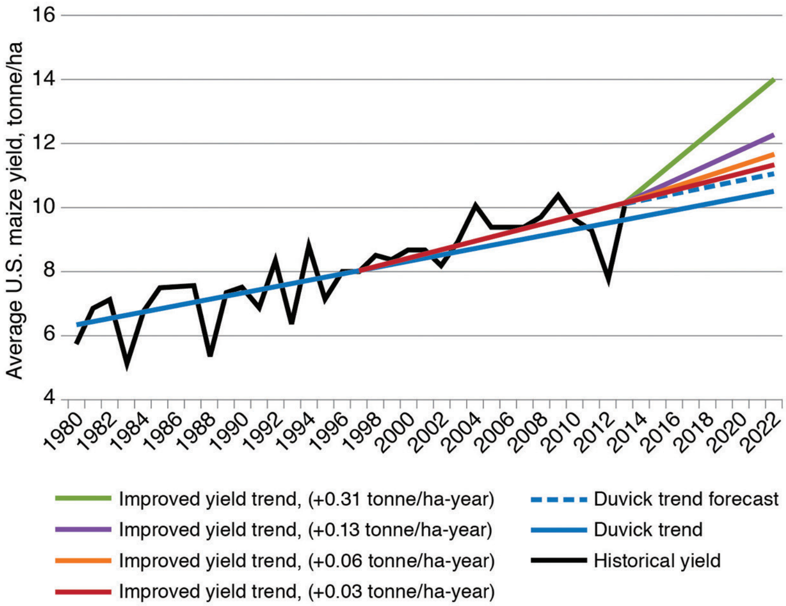

FIGURE 4-3 Historical and projected maize grain yields in the United States.
SOURCE: Leibman et al. (2014).
NOTE: Blue solid line indicates trends proposed by Duvick (2005) for historical annual increases in grain yield of 0.10 tonne/ha-year. Purple line indicates trend of larger average annual increases (0.13 tonne/ha-year) in grain yield since adoption of GE maize in 1996. Dotted blue line indicates a return to previous historical average annual increases (0.10 tonne/ha-year) in grain yield in the future. Red, orange, and light green lines represent forecasts of improved yield trends of 0.06–0.31 tonne/ha-year over and above historical average of 0.10 tonne/ha-year.

EFFECTS RELATED TO THE USE OF *Bt* CROPS

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.

Yield Effects of Genetically Engineered Insect Resistance

As of 2015, IR traits had been incorporated into maize, cotton, eggplant, and poplar. This section relies in part on past reviews of the literature, but these reviews typically do not provide the reader with an understanding of technical caveats associated with the reviewed studies. There is continuing controversy over claims about yield effects of GE insect-resistant crops, and the committee received a number of public comments related to this. Therefore, in addition to relying on review articles, the committee also examined a substantial number of original research articles to carefully assess the quality of data that has been used to support various claims.

Bt Maize

Meta-analyses and summary reports that included an examination of *Bt* maize production in different parts of the world were reviewed. Areal et al. (2013) compared yields of *Bt* maize with those of the non-*Bt* counterparts. On the basis of data collected from the Philippines, South Africa, the United States, Spain, Canada, and the Czech Republic, Areal and colleagues found that *Bt* maize yielded 0.55 tonne/hectare more than maize without *Bt*. Areal et al. (2013:27) were careful to point out that "although it cannot be discerned whether the advantages of cultivating [genetically modified] GM crops were due to the technology itself or to farmers' managerial skills (GM adopter effect), the GM adopter effect is expected to diminish as the technology advances" because early adopters are typically farmers with better managerial skills (and resources), and over time farmers with a mix of managerial skills will use the technology.

A review by Fernandez-Cornejo et al. (2014) found a yield advantage of *Bt* maize over non-*Bt* maize in all the surveys (four) and experiments (five) that they examined that were conducted in 1997–2003 in the United States. However, a different analysis that used yield data from South Africa, Germany, and Spain collected from 2002 to 2007[5] did not identify a difference between the yields of *Bt* and non-*Bt* maize overall or in each of the three countries separately (Finger et al., 2011). Neither the *Bt* trait used nor the insect pest targeted was specified in the studies because they looked at findings from a number of locations.

Gurian-Sherman (2009) reviewed results of studies conducted in the United States and Canada on effects of GE traits on maize and soybean yield. With regards to maize, he reviewed six studies published in 1997–2004 and concluded that the *Bt* traits to resist European corn borer (*Ostrinia nubilalis*) closed the yield gap by 7–12 percent in locations where infestation by the insect was high.[6] On the basis of review of three additional studies in Iowa published in 2005–2008, he concluded that the *Bt* trait targeting corn rootworm (*Diabrotica* spp.) substantially decreased the yield gap in situations where insect-pest pressure was high and water

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[5] Yield data from Spain in 1997 were also included.

[6] Gurian-Sherman (2009) estimated that high levels of European corn borer infestation occurred on 12–25 percent of U.S. maize acres, on the basis of Rice and Ostlie (1997).

availability was low. In situations without those constraints, the *Bt* traits for either pest did not have an effect on yield. Gurian-Sherman (2009) estimated that *Bt* maize production in general brought U.S. maize 3–4 percent closer to its potential yield. Klümper and Qaim (2014) conducted a large meta-analysis on the effects of GE crops, including those with *Bt* traits. They did not segregate their results by crop, but in aggregate they found that yields of maize and cotton were 22 percent greater when a *Bt* trait was present (n=353).

The reviews and meta-analyses cited above make clear that benefits associated with crops with *Bt* traits vary substantially and depend on insect-pest abundance in the area of the survey or experiment. It is not clear from the broad literature surveys whether differences in yields are due solely to the *Bt* traits' reducing of insect-pest damage or to differences among the farmers who use the varieties and other agronomic differences among the varieties (see also Box 6-1). Therefore, the committee looked carefully at studies of maize with and without *Bt* traits that were conducted since initial commercialization because these studies allow one to assess the role of insect-pest abundance and the genetic background of the crop varieties tested. The committee includes here a set of specific studies that it found to be most informative regarding the factors that influence if and how much the *Bt* trait decreases yield gaps.

Bowen et al. (2014) compared seven pairs of *Bt* maize hybrids and their non-*Bt* counterparts at several sites in Alabama. They also included a comparison between a maize hybrid with one *Bt* trait and its isogenic[7] counterpart with two *Bt* traits. The study was conducted from 2010 to 2012. In southern parts of the United States, the insect targets of *Bt* hybrids are primarily corn earworm (*Helicoverpa zea*) and fall armyworm (*Spodoptera frugiperda*). Infestations of corn earworm and fall armyworm were variable over that time. Bowen and colleagues found that yields were greater in *Bt* maize than in non-*Bt* maize in 2 of the 3 years. However, there was not a clear relationship between the amount of insect-pest damage and the yield improvements due to *Bt* because the year with the greatest pest damage (2010) had intermediate yield improvements.

Reay-Jones and Reisig (2014) conducted field studies in which corn earworm was the target pest. At two sites, one in North Carolina and one in South Carolina, they planted near isolines of non-*Bt* maize and maize with one to three *Bt* traits in 2012 and 2013. They did not find differences in yields between near isolines with and without *Bt* traits. They noted

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[7] An *isogenic line* has closely related genotypes of a crop that differ by one or a few genes and are therefore expected to perform similarly on farms. *Near isogenic lines* (or *near isolines*) are more vaguely defined and can have multiple genes differing between them and thus may have differences in performance under some farm conditions.

that similar results were found in the southeastern United States in maize planted at recommended times (Buntin et al., 2001, 2004; Allen and Pitre, 2006; Reay-Jones et al., 2009; Reay-Jones and Wiatrak, 2011). Because the targeted insect did not cause much damage in the region, they concluded that *Bt* traits aimed at corn earworm may not close the gap between actual yield and potential yield.

In experiments conducted soon after *Bt* maize commercialization in Canada and in the Midwest and Northeast growing areas of the United States where European corn borer populations typically caused yield losses in non-*Bt* maize, increased *Bt* maize yields were shown to be clearly associated with decreased insect-pest damage. Baute et al. (2002) concluded that in the Canadian Midwest, European corn borer infestations resulted in 6- and 2.4-percent reductions in yield for 1996 and 1997. In experiments in four to six locations per year in Pennsylvania and Maryland in 2000, 2001, and 2002, Dillehay et al. (2004) found that the average yields of *Bt* maize varieties and their non-*Bt* isolines were 9.1 and 8.6 tons/hectare, respectively (a 5.8-percent difference). Yield per plant in the non-*Bt* isolines was reduced by 2.37 percent per corn borer tunnel in the plant.

Between the 1996 introduction of *Bt* maize and 2009, European corn borer populations and the damage that they cause decreased dramatically, as documented by Hutchison et al. (2010). The decline appears to have continued to a point where the European corn borer adults can be difficult to find in the Midwest (Box 4-2). In a study throughout Pennsylvania in 2010, 2011, and 2012, at 16, 10 and 3 farm sites, respectively, Bohnenblust et al. (2014) planted *Bt* and non-*Bt* varieties. The populations of European corn borer was low throughout the area studied; in only three of the sites were insect densities great enough to cause a 3-percent yield loss in non-*Bt* hybrids. Overall, yield of the *Bt* varieties was 1.9 percent greater than that of the non-*Bt* varieties. Some of the small difference could be explained by insect pest pressure, but some of the difference could also have been due to differences in other characteristics of the varieties. As with the experiments in Pennsylvania, most current differences in yield between *Bt* and non-*Bt* varieties in the Midwest are unlikely to be caused by this once important insect pest.

Field experiments in Nebraska in 2008, 2009, and 2010 compared glyphosate-resistant maize hybrids that also had *Bt* traits targeting European corn borer and corn rootworm with genetically similar hybrids without the *Bt* traits "in environments with no detectable infestation [of European corn borer or corn rootworm] based upon visual observations in-season and during harvest" (Novacek et al., 2014:94). Therefore, any differences in yield could not be attributed to effects of the *Bt* toxins. The density of maize plants in the different test plots was 49,300–111,100 plants/hectare. The hybrids with *Bt* traits yielded about 5 percent more than their counter-

BOX 4-2
Regional Suppression of Pests Through Widespread Adoption of *Bt* Varieties

In areas of the United States where adoption of either *Bt* maize or *Bt* cotton is high, there is statistical evidence that insect pest populations are reduced—a benefit to both adopters and nonadopters of *Bt* crops. Carrière et al. (2003) demonstrated that in areas of Arizona where over 65 percent of the cotton had a *Bt* trait in 1999–2001 there was a decline in the population density of pink bollworm (*Pectinophora gossypiella*) compared with population density in 1992–1995, before *Bt* cotton was commercialized. In 2006, the combined use of *Bt* cotton, release of sterile bollworm, and early stalk destruction resulted in the elimination of pink bollworm from Arizona (Liesner, 2015). Adamczyk and Hubbard (2006) found over a 90-percent decline in tobacco budworm (*Heliothis virescens*) populations in the Mississippi Delta associated with the planting of *Bt* cotton; Micinski et al. (2008) found similar reductions in Louisiana.

Wu et al. (2008) demonstrated similar suppression of cotton bollworm (*Helicoverpa armigera*) in China and attributed it to the adoption of *Bt* cotton beginning in 1997. The suppression due to *Bt* cotton decreased damage not only in cotton but in other crops.

Hutchison et al. (2010) demonstrated a dramatic area-wide suppression of European corn borer in a five-state area (Iowa, Illinois, Minnesota, Nebraska, and Wisconsin) where *Bt* maize was planted widely. They concluded that farmers who planted non-*Bt* maize were profiting more than those who planted *Bt* maize because of the decline in the regional population of corn borers. The decline in the European corn borer in those states and in the mid-Atlantic region (Bohnenblust et al., 2014) has continued to a point where the insect is rarely a pest in many counties. In 2014, a survey in Wisconsin found that 193 of 229 maize fields showed no evidence of corn borer infestation; on the average, only 3 percent of stalks were infested, and the average expected yield loss was less than 0.09 percent (WI Department of Agriculture, 2014).

parts in 2008, but no difference in yield was observed in 2009 or 2010. The increased yield in 2008 was not explained by damage to the non-*Bt* hybrids caused by the target insect pests to the non-*Bt* hybrids.

In Illinois, Haegele and Below (2013) compared two sets of locally adapted maize hybrids with the same general genetic backgrounds in the growing seasons of 2008 and 2009. In each set, one hybrid had GE resistance to glyphosate and the other had the GE trait for glyphosate resistance and *Bt* traits for resistance to European corn borer and corn rootworm. Each hybrid was grown with several rates of nitrogen fertilization. Root damage was measured in 2008 and inferred in 2009. The authors stated that "based on these low levels of apparent root injury, few differences in grain yield or agronomic performance between non-*Bt* and *Bt* hybrids might be expected" (Haegele and Below, 2013:588). Nevertheless, averaged over all rates of nitrogen fertilization, yields were greater in the *Bt* hybrids than in the comparable non-*Bt* hybrids: about a 7-percent difference in one set and an 18-percent difference in the other.

Another study in Illinois examined insect resistance as one of five factors that might contribute to yield of maize (Ruffo et al., 2015). Maize with only glyphosate resistance was compared with its near isoline that contained *Bt* targeting European corn borer and corn rootworm. The other four factors tested were density of maize plants per unit area, strobilurin-containing fungicide, application of a combined phosphorus–sulfur–zinc fertilizer, and application of nitrogen fertilizer. In field trials on two sites during the 2009–2010 growing season, they compared effects of near isolines with and without the *Bt* toxins. When all other factors were maximal for increased yield, the *Bt* hybrids had 8.7 percent greater yield. When none of the other factors was optimized for yield the *Bt* hybrids had 4.5 percent greater yield. The authors hypothesized that adult corn rootworm feeding on silks may have influenced kernel formation and affected yield, but insect data were not presented, so it was difficult to determine whether corn rootworm had any effect. European corn borer numbers in Illinois were very small in 2009 and 2010 (Hutchison et al., 2010; Box 4-1).

Nolan and Santos (2012) compiled results of maize hybrid trials conducted by land-grant universities in the 10 leading maize-producing U.S. states from 1997 to 2009. For hybrids that had herbicide resistance, they found yield increases for maize with *Bt* resistance to European corn borer and for maize with *Bt* targeting corn rootworm compared with non-GE hybrids. Maize with *Bt* targeting European corn borer yielded 6 percent more than non-GE hybrids on the basis of data from 1999–2009 (fixed-effects model); maize with *Bt* targeting corn rootworm yielded 7.4 percent more on the basis of data from 2005–2008. The yield difference was 7.1 percent when the two traits were present in the same variety on the basis of data from 2005–2009. No data were presented on rate of insect-pest infestation, although the authors stated that infestations of European corn borer were decreasing, which is consistent with surveys in the region.

Shi et al. (2013) used a time-series analysis of experimental data on small plots in Wisconsin (1990–2010) to assess changes in yield and variability of yield. They found that the average yield in all years for maize with a *Bt* trait targeting European corn borer was greater (410 kilograms/hectare) than for non-GE maize. However, the average yield was less (765 kilograms/hectare) for *Bt* maize with resistance to corn rootworm. The *Bt* trait for European corn borer reduced yield in the early years of the survey but increased yield in later years even though the population of the pest had declined. Shi et al. (2013) concluded that for some traits there is yield drag initially, but with continued breeding the effect is decreased or reversed. A reversal could explain results of other experiments described above in which a hybrid with a *Bt* trait outperformed a non-*Bt* hybrid even without insect-pest pressure. Although yield was adversely affected by the *Bt* trait for rootworms during the period through 2010 examined by Shi et al. (2013), this may no longer be the case.

In the Brazilian state of Santa Catarina, Ozelame and Andreatta (2013) found a maize hybrid with *Bt* targeted at corn earworm and several other pests to yield 6.89 percent better than the non-*Bt* near isoline, but no statistical analysis was conducted. The study was conducted in the harvest of 2010–2011. A study in the Philippines in the wet season of 2010 reported that yields in the Isabela province did not differ statistically between *Bt* and non-*Bt* maize (Afidchao et al., 2014). Gonzales et al. (2009) conducted surveys of *Bt* and non-*Bt* maize in the Philippines and conclude that *Bt* maize had yield increases of 4–33 percent. Because no statistical analysis was provided, it was not possible to quantitatively assess the results.

One of the claims regarding *Bt* crops is that they would stabilize yield or, more accurately, would limit the risk of a farmer having dramatic yield loss (crop failure). Given that the *Bt* trait increases yield more when there is high insect pressure, it seems intuitive that it would diminish crop failure under severe insect-pest pressure. The committee was able to find only three peer-reviewed studies specifically focused on quantifying *Bt* crop contributions to avoiding crop loss. Crost and Shankar (2008) examined variation in farm yields of *Bt* and non-*Bt* cotton. In India they found a clear decrease in variance, but in South Africa no difference was shown. Shi et al. (2013) examined maize yields in research plots in Wisconsin, where mean yield was 11,650 kilograms/hectare. They found that varieties with *Bt* toxins for European corn borer and western corn rootworm had decreased "cost of risk" of 106.5 kilograms/hectare. Working with cotton farmers in India, Krishna et al. (2016) found that lower variance in *Bt* cotton yield, especially on the low end, increased average yield by 2.5 percent.

In 2008, USDA's Risk Management Agency concluded that the "Monsanto Company, as a co-submitter of the pilot BYE, has demonstrated that its specific triple-stack genetic traits, when used in combination, provide lower yield risk as compared to non-traited hybrids."[8] The BYE (Biotechnology Yield Endorsement) program provided farmers with discounted crop insurance if they planted maize with *Bt* traits that targeted Lepidoptera and corn rootworm along with the GE trait for glyphosate resistance. The discount was based on the expectation that there was a lower risk of crop failure with these varieties. The program ended in 2011.

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[8] RMA approves BYE for 2008 implementation. January 3, 2008. Available at http://www.rma.usda.gov/news/2008/01/102bye.html. Accessed March 17, 2016.

Bt Cotton

The meta-analysis conducted by Areal et al. (2013) found that on the average cotton containing *Bt* yielded 0.30 tonne/hectare more than cotton without *Bt*. Their finding was based on data collected from India, China, South Africa, Argentina, Mexico, and Australia in 1996–2007. They concluded that there is a greater advantage to *Bt* cotton in developing than in developed countries. The analysis conducted by Finger et al. (2011) used data from the United States, China, Australia, India, and South Africa. Yield data were reported for 1995–2007 from 237 studies that included *Bt* cotton and 195 studies that included non-*Bt* cotton. Areal et al. (2013) provided a list of the studies used, but Finger et al. (2011) did not, so it is not possible to know whether they used the same studies. When the studies in Finger et al. (2011) are separated by country, the yield advantage for *Bt* cotton is different for India, where the yield was 50.8 percent greater. The authors concluded that the reason that India's yield advantage was much larger than that of the others (particularly the United States and Australia) was that when *Bt* cotton was commercialized in India in 2002, it introduced insect control to production areas that had had little or none. The authors cautioned that yield advantages within India may depend on the specific location.

Stone (2011) critiqued studies that showed yield increased in India directly after *Bt* cotton was approved in 2002 and that did not control for the bias whereby early adopters of new technology usually have more assets than later adopters or nonadopters (for more on the assets of early adopters, see section "Income Effect of Early Adoption" in Chapter 6). However, studies performed in years after *Bt* cotton was introduced and widely adopted[9] found yield advantages. In the Indian state of Madhya Pradesh, Forster et al. (2013) compared cotton production over two seasons (2007–2008 and 2009–2010) in four farming systems: *Bt*, non-*Bt*, organic, and biodynamic.[10] In the 2007–2008 season, the system with *Bt* had 16-percent higher yield than the isogenic non-*Bt* system; in the 2009–2010 season, the system with *Bt* had 13.6-percent higher yield. In this experimental study, the *Bt* cotton had about 8-percent higher total

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[9] In 2006, *Bt* cotton was grown on 3.8 million hectares of land in India, which was 42 percent of its land in cotton production that year (James, 2006). In 2008, those numbers had grown to 7.6 million hectares, or 82 percent of cotton production (James, 2008); by 2010, *Bt* cotton was grown on 9.4 million hectares, or 86 percent of the land in cotton production (James, 2010).

[10] Forster et al. (2013) described biodynamic farming systems this way: "Preparations made from manure, minerals and herbs are used in very small quantities to activate and harmonize soil processes, to strengthen plant health and to stimulate processes of organic matter decomposition. Most biodynamic farms encompass ecological, social and economic sustainability and many of them work in cooperatives."

nitrogen fertilizer input but was harvested earlier, in accord with government recommendations for higher inputs for *Bt* cotton. Forster et al. (2013) commented that the differences might have been more modest in their experiment than in surveys because the insect-pest problems in non-GE cotton were managed better in their experiment than in typical farms.

Kathage and Qaim (2012) surveyed cotton farmers in the Indian states of Maharashtra, Karnataka, Andhra Pradesh, and Tamil Nadu in 2002, 2004, 2006, and 2008. Controlling for all other factors, they found *Bt* cotton that controlled cotton bollworm (*Helicoverpa armigera*) had a yield advantage of 51 kilograms/hectare, a 24-percent increase over non-GE cotton yields during the period of the study. Their analysis led them to conclude that per-hectare yield benefits probably increased from 2002–2004 to 2006–2008. They hypothesized that the growth in yield advantage could be attributed to the increase in the availability of varieties with *Bt* starting in 2006 and the introduction of new *Bt* traits to the market around the same time.

A meta-analysis of 19 studies conducted in India with data from 2002 to 2008 reported that *Bt* cotton had a 33-percent yield advantage per hectare over non-*Bt* cotton (Witjaksono et al., 2014).[11] Stone (2011) found an average yield increase of 18 percent from 2003, when no *Bt* cotton was planted by the farmers sampled in four villages, to 2007, when farmers in the same villages planted *Bt* cotton almost exclusively. However, he noted that yields in Andhra Pradesh, the state where the villages were, did not so much increase as return to the peak that was achieved in 1994. Romeu-Dalmau et al. (2015) also raised the issue of whether the type of cotton grown could play a part in yield outcomes. They compared *Bt* cotton *G. hirsutum* L. with non-*Bt* cotton *G. arboretum*, a variety commonly grown in India before a U.S. variety of *G. hirsutum* was introduced in the 1980s. The authors interviewed 36 farmers who operated less than 5 hectares of land. Under rain-fed conditions in Maharashtra, India, yields for *Bt G. hirsutum* were not greater.

In a survey of cotton farmers in Punjab, Pakistan—248 of whom grew *Bt* cotton and 104 non-*Bt* cotton—Abedullah et al. (2015) reported a yield advantage of 26 percent for farmers of *Bt* cotton. The study was conducted from December 2010 to February 2011, the first cotton-growing season after Pakistan approved commercial planting of *Bt* cotton. As part of the study, they examined farmer assets. Their findings were consistent with Stone's (2011) point that early adopters have more assets. *Bt* adopters were different in several ways: they had more education, more land, and more access to credit. They also were more likely to own a tractor and to have been aware of *Bt* cotton before nonadopters.

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[11] Data collected by Kathage and Qaim (2012) and Stone (2011) were included in this meta-analysis.

A meta-analysis of 17 studies conducted in China with data from 1999 to 2005 reported that *Bt* cotton had an 18.4-percent yield advantage (480 kilograms/hectare) over non-*Bt* cotton (Witjaksono et al., 2014). Surveys of 500 farmers conducted by the Center for Chinese Agricultural Policy in two cotton-growing regions in 2004, 2006, and 2007 reported that mean yields of *Bt* cotton were at least 500 kilograms/hectare greater than non-*Bt* cotton yields (Pray et al., 2011). In 2006, however, only 14 farmers reported growing non-*Bt* cotton, and the number had shrunk to four in 2007, so the reported differences were not robust. Qiao (2015) looked at the yield effect of *Bt* cotton throughout China since its introduction and found that it had a positive effect on yield that was stable from the adoption of *Bt* cotton in 1997 through the end of the study in 2012.

Cotton is a major cash crop for Burkina Faso. Although its production is much smaller than that of the world's largest producers (China and India), Burkina Faso was the 10th-largest producer of cotton in 2013. *Bt* cotton was introduced there commercially in 2008. In an experiment conducted before commercialization on two sites in 2003, 2004, and 2005, Héma et al. (2009) compared a U.S.-developed *Bt* cotton containing the endotoxins Cry1Ac and Cry2Ab with three other treatments: a non-*Bt* local variety with standard insecticide applications, a non-*Bt* local variety without insecticide application, and a U.S. non-*Bt* variety without insecticide application. The *Bt* toxins in the GE variety targeted cotton bollworm and cotton leafroller (*Syllepte derogate*). Yields varied in space and time. At one site, the *Bt* variety had greater yields of seed cotton than the other tests in 2003. In 2004, there was no difference among the four varieties. The authors posited that differences were lacking in that year because insect-pest pressure was low. In 2005, yields from the *Bt* and insecticide-treated local varieties were statistically equivalent and yielded significantly more than the other two varieties. At the other site, the yields of the *Bt* variety and treated local variety were equivalent and were greater than the yields of other two varieties in all 3 years.

A survey of 160 rural households in 10 villages in the three cotton-growing regions of Burkina Faso was conducted in 2009, when roughly 30 percent of cotton hectares were planted with *Bt* cotton. Vitale et al. (2010) reported that there was an average yield advantage of 18.2 percent for *Bt* cotton over non-*Bt* cotton in all three regions. There was statistical interaction between the yield advantage and the specific region; the greatest advantage was 36.6 percent and the least was 14.3 percent. The authors hypothesized that the range in yield effect was due to differences in insect-pest populations among the regions. By 2012, *Bt* varieties were planted on 51 percent of cotton hectares in Burkina Faso (James, 2012).

Fernandez-Cornejo et al. (2014) reviewed three experiments and six surveys of *Bt* cotton production in the United States published in 1997–

2007. Greater yield of *Bt* than non-*Bt* varieties was reported in two of three experiments and in all surveys. The authors offered a caveat about survey results because "*Bt* use is not random. Surveyed farmers are not randomly assigned to a treatment group (adopters) and a control group (nonadopters). Consequently, adopters and nonadopters may be systematically different from one another (for example, in terms of management ability)."

Luttrell and Jackson (2012) compiled data on U.S. cotton crop loss to insects in 2000–2007. The estimated average of the percentage of crop loss to all insects (targets and nontargets of *Bt*) was lower for *Bt* cotton than for non-GE cotton (4.13 percent versus 6.46 percent), but no difference in yield between *Bt* and non-GE cotton was identified. Kerns et al. (2015) evaluated yields of one non-*Bt* variety and four *Bt* varieties of cotton in field plot tests in Arkansas, Louisiana, Mississippi, and Tennessee in 2014. When all varieties were sprayed for caterpillars, the *Bt* varieties still had a yield advantage of 9–52 percent, depending on location.

Bt Eggplant

As of 2015, *Bt* eggplant (*Solanum melongena*) was grown commercially only in Bangladesh. It was engineered for resistance to fruit and shoot borer (*Leucinodes orbonalis*) and first commercialized in spring 2014, when 20 farmers in four regions planted one of the four *Bt* varieties of eggplant (locally known as brinjal) on a total of 2 hectares (Choudhary et al., 2014). Krishna and Qaim (2008) summarized data provided to them from research-managed field trials conducted by MAHYCO, a seed company, but none of the data was published. In several Indian states during the mid-2000s, they found yield of uninfected fruit to be 117 percent greater in *Bt* eggplant hybrids than in insecticide-treated isogenic non-*Bt* hybrids. When the *Bt* hybrids were compared by the company with popular open-pollinated varieties of eggplant, the yield benefit grew to 179 percent. Krishna and Qaim predicted that under field conditions the yield advantage of *Bt* eggplant hybrids over non-*Bt* hybrids would be 40 percent and over open-pollinated varieties 60 percent. Results of large-scale field trials conducted by the Indian Institute of Vegetable Research during 2007–2008 and 2008–2009 were similar. Seven *Bt* eggplant hybrids were planted in eight locations alongside non-*Bt* hybrids. When *Bt* hybrids were compared with the non-*Bt* varieties into which the *Bt* trait had been introgressed, the yield of the *Bt* hybrids was 37.3 percent more than that of the non-*Bt* hybrids, but no statistics were presented. The yield increased to 54.9 percent when the comparison was with other popular hybrids, but again no statistics were presented (Kumar et al., 2010). The yield gains in both studies were due to the reduced damage from fruit and shoot borer. Andow (2010) argued that losses in non-*Bt* eggplant for subsistence farmers were not as high as other studies had estimated because these farmers have outlets for selling or consuming damaged fruit, whereas large-scale commercial farmers do not.

Bt Poplar Trees

Poplar trees with *Bt* have been planted in China since field testing began in 1994, but they were not approved for commercialization until 2005. *Populus nigra* has been genetically engineered with *Bt* toxins targeted at poplar looper (*Apochima cinerarius*) and clouded drab moth (*Orthosia incerta* Hufnagel) (Hu et al., 2001). Although poplar can be grown for fuel, fiber, and forest products, poplar plantations in China have been used primarily to provide environmental protection and afforestation in northern China (Hu et al., 2001; Sedjo, 2005). Therefore, yield effects have not been an outcome of interest in the study of *Bt* poplar in China.

Field trials elsewhere have found some effect on yield of *Bt* traits in poplar in which *Bt* genes were inserted into specific clonal lines. In a screening trial of four paired clonal lines of poplar (one *Populus deltoides* × *Populus nigra* hybrid and three *Populus trichocarpa* × *Populus deltoides* crosses) in the Pacific Northwest of the United States, plant growth in three of the clonal lines with *Bt* gene insertion (expressing Cry3Aa) was not substantially different from that in their paired non-*Bt* line (Klocko et al., 2014). The average volume growth of one of the *Bt Populus trichocarpa* × *Populus deltoides* crosses was greater than its control based on measurements in year-1 and year-2. After the screening trial, the *Populus deltoides* × *Populus nigra* hybrid was used in a large-scale trial. From season 1 to season 2, net volume growth in *Bt* trees was an average of 8 percent greater than that in the controls (Klocko et al., 2014). Hjältén et al. (2012) compared aspen (*Populus tremula* × *Populus tremuloides*) clones expressing *Bt* toxins with isogenic non-*Bt* clones. The trees were planted in pots in a greenhouse. The authors found that the *Bt* trees were shorter than the non-*Bt* clones in the absence of the targeted insect, brassy willow-leaf beetle (*Phratora vitellinae*). However, the *Bt* trees were taller when beetle populations were great enough to cause substantial defoliation. Thus, there is evidence that GE insect resistance addresses yield-reducing factors in trees.

> **FINDING: Although results are variable, *Bt* traits available in commercial crops from introduction in 1996 to 2015 have in many locations contributed to a statistically significant reduction in the gap between actual yield and potential yield when targeted insect pests caused substantial damage to non-GE varieties and synthetic chemicals did not provide practical control.**

FINDING: In areas of the United States where adoption of *Bt* maize or *Bt* cotton is high, there is statistical evidence that insect-pest populations are reduced regionally, and the reductions benefit both adopters and nonadopters of *Bt* crops.

FINDING: In surveys of farmers' fields, differences in yield between *Bt* and non-*Bt* varieties may be due to differences between the farmers who do and who do not plant the *Bt* varieties. These differences could inflate the apparent yield advantage of the *Bt v*arieties if *Bt*-adopting farmers on the average have other production advantages over non-*Bt*–adopting farmers.

FINDING: In experimental plots, the difference in yield between *Bt* and non-*Bt* varieties is sometimes demonstrated to be due to decreased insect damage to the *Bt* variety, but in cases in which comparisons are not between true isolines, differences may be due to other characteristics of the *Bt* varieties or to a combination of crop variety and decreased insect-pest damage. These differences could confound the estimation of the apparent yield advantage of the *Bt* varieties.

RECOMMENDATION: In future experimental and survey studies that compare crop varieties with IR traits with those 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 factors.

Changes in Insecticide Use Due to Insect-Resistant Crops

There have been numerous studies of changes in insecticide use on large-scale and small-scale farms as a result of the adoption of crops that produce *Bt* toxins. There is no question of whether GE crops have changed the amounts of insecticides used by adopting farmers. The debate is over the magnitude and direction of the changes. The meta-analysis by Klümper and Qaim (2014), for example, documented a 39-percent reduction of insecticide quantity from the adoption of *Bt* cotton and maize (n=108). The 2010 National Research Council report on impacts of GE crops in the United States reviewed data from USDA on insecticide use in cotton and maize from 1996 through 2007 and found a clear pattern of decline in both crops in pounds of active insecticidal ingredient (a.i.) applied per acre (NRC, 2010a).[12] Fernandez-Cornejo et al. (2014) extended the assessment

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[12] For example, pounds of a.i. applied per acre dropped from 0.23 in 1996 to 0.05 in 2007 for maize and from 1.6 in 1996 to 0.7 in 2007 for cotton.

of USDA data through 2010 as illustrated in Figure 4-4. They also found that the reduction was apparent for both adopters and nonadopters of *Bt* maize (Figure 4-5). The decrease for nonadopters could be due to the regional decline in European corn borer populations (see Box 4-2).

A survey of farmers in the Philippines (Sanglestsawai et al., 2014) found that the amount of insecticide used on *Bt* maize was one-third and one-fourth of the amount used on non-*Bt* maize in the two growing seasons analyzed (2003–2004 and 2007–2008).

The committee did not find studies on the effects of *Bt* maize on insecticide use on small farm situations, presumably because insecticides are not typically used on the non-GE maize on these farms.

In Australia, the adoption of *Bt* cotton was slower than in the United States because, in efforts to slow the evolution of insect pests resistant to *Bt*, the Australians limited farms to planting 30 percent of their area in *Bt* cotton until 2003, when the single *Bt* toxin variety INGARD® was replaced with a two-toxin variety Bollgard® II. As can be seen in Figure 4-6, there has been a dramatic decline in insecticide use in Australia both in *Bt* cotton and in non-*Bt* cotton (Wilson et al., 2013).

Adoption of *Bt* cotton in China was rapid: The percentage of farmland planted to *Bt* cotton rose to more than 95 percent by 2011 (Lu et al., 2012). The increase in use of *Bt* cotton resulted in reduced density of the target pest, *Helicoverpa armigera*, and to a decrease in overall use of insecticide on cotton (Figure 4-7).

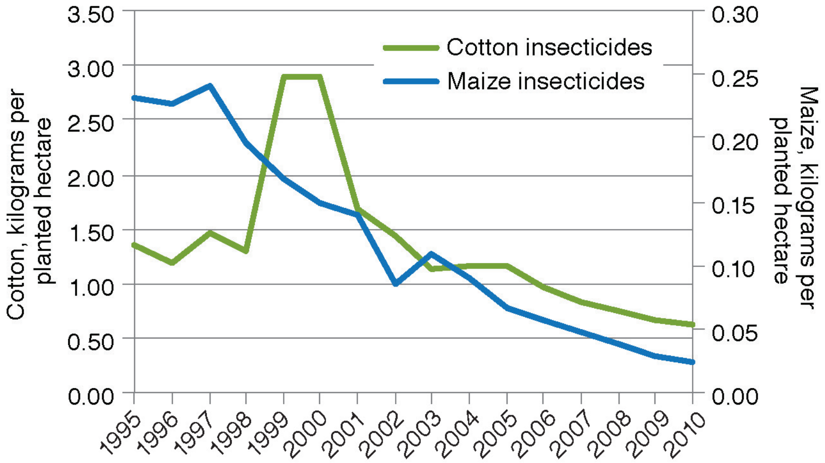

FIGURE 4-4 Rates of insecticide application for maize and cotton in the United States from 1995 to 2010.
SOURCE: Fernandez-Cornejo et al. (2014).

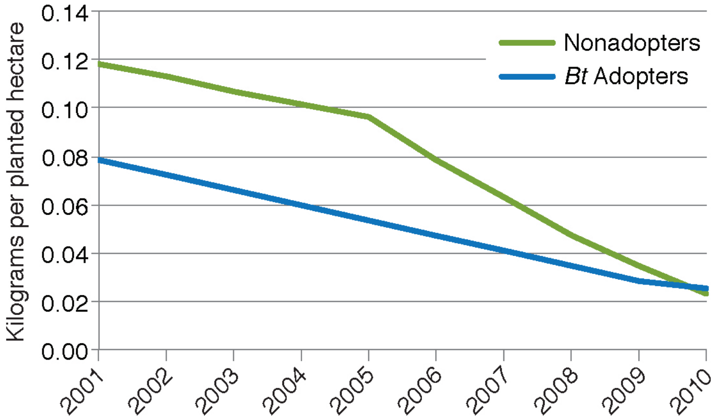

FIGURE 4-5 Rates of insecticide application by adopters and nonadopters of *Bt* maize in the United States from 2001 to 2010.
SOURCE: Fernandez-Cornejo et al. (2014).

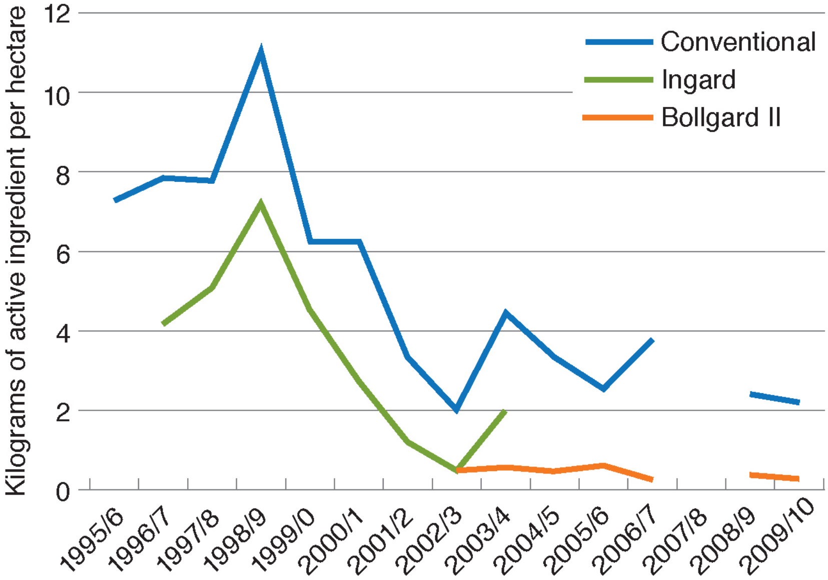

FIGURE 4-6 Insecticide use on non-*Bt*, Ingard®, and Bollgard II® *Bt* cotton in Australia.
SOURCE: Wilson et al. (2013).
NOTE: No data were collected in 2007–2008 because the cotton area was small owing to drought.

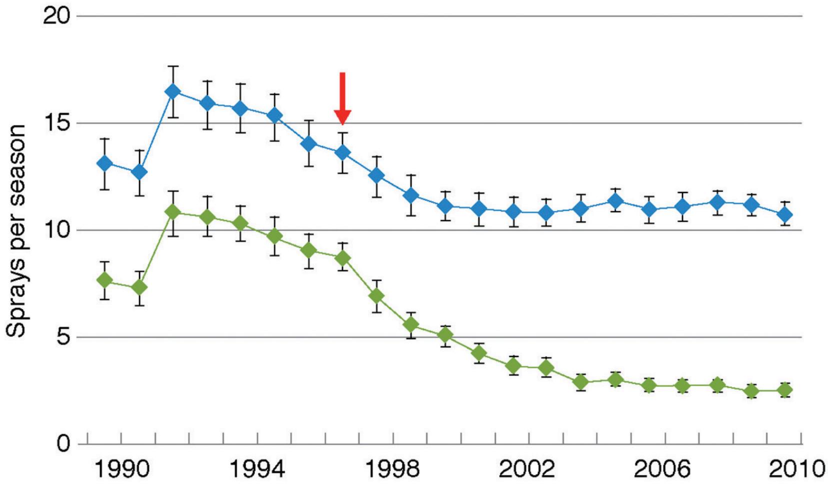

FIGURE 4-7 Number of sprays of insecticide on cotton per season in China.
SOURCE: Lu et al. (2012).
NOTE: Blue dots are total insecticide; green dots are insecticide spray aimed at cotton bollworms. Red arrow indicates the year when *Bt* cotton was first commercialized.

The changes in insecticide applications resulting from the adoption of *Bt* cotton in India have been the subject of numerous studies, beginning around 2000 when availability of *Bt* seeds became widespread. Qaim and Zilberman (2003) analyzed data from field trials in 2001 and found that the amount of insecticide applied by *Bt* adopters was 69 percent less than by nonadopters (1.74 and 5.56 kilograms/hectare, respectively). Those results were extended by Sadashivappa and Qaim (2009), who found that average insecticide application on *Bt* cotton was 41 percent of that on non-*Bt* cotton, and by Kouser and Qaim (2011), who documented a 64-percent difference. Kouser and Qaim also showed that aggregate insecticide application declined for nonadopters of *Bt* cotton during the same period (they did not delineate pesticide categories—insecticides versus other pesticides). Similar results were reported by Stone (2011); the number of insecticide sprays applied by cotton growers in the Warangal District of Andhra Pradesh, India, fell by a statistically significant amount—more than half (54.7 percent)—from 2003 to 2007, with the largest reductions in areas with the greatest insecticide use.

Shankar et al. (2008) studied the relationship between insecticide use and *Bt* cotton in South Africa and found that farms using *Bt* cotton applied insecticide at 1.6 liters/hectare, and those with non-*Bt* cotton applied 2.4 liters/hectare.

Even though overall use of insecticides on maize and cotton in the United States has decreased, since 2003 there has been a substantial increase in treatment of maize, cotton, and soybean seed with neonicotinoid insecticides (Thelin and Stone, 2013). The committee received comments from the public that suggested that the increase could have been due to or associated with the increase in use of *Bt* crops. Douglas and Tooker (2015) provided a detailed assessment of U.S. data on the increase in use of neonicotinoids from the 1990s until 2011. It is clear that the increase was as dramatic in soybean as in maize. As of 2015, commercial soybean in the United States had not been engineered to produce *Bt* toxins, so the increase in neonicotinoid use in this crop clearly was not associated with the use of *Bt* varieties. Increases in use of neonicotinoids have also been seen in vegetables and fruits that are not genetically engineered. In the case of maize, the rates of use of neonicotinoids on seeds are too low to affect rootworms, and the *Bt* toxin in maize roots seems to affect only rootworms, so *Bt* and neonicotinoid insecticides act mostly as complementary pest-management tools (Petzold-Maxwell et al., 2013; Douglas and Tooker, 2015). However, another study suggested that a seed treatment could affect rootworm survival and might interact with *Bt* maize (Frank et al., 2015), so the potential for synergy between the two kinds of compounds in causing rootworm mortality should be further investigated. That overall insecticide use in maize and cotton has decreased even with the increase in use of neonicotinoid seed treatments is due in part to the fact that only about 0.001 kilogram of active ingredient of neonicotinoid is used per hectare[13] and data on kilograms of seed-treatment chemicals do not seem to be reported in insecticide surveys conducted by USDA–NASS (Douglas and Tooker, 2015). One commonality between the use of *Bt* crops and the use of neonicotinoids is that the farmer's decision to use either of them must be made before the beginning of the season, so use is prophylactic. Furthermore, farmer choice is sometimes constrained because most maize and cotton seed that is available is likely to produce at least one *Bt* toxin and be treated with a neonicotinoid insecticide.

Although there is an overall reduction in the amount of synthetic insecticides used as a result of planting of *Bt* crops, Benbrook (2012) pointed out that a hectare of maize planted with a variety that has multiple *Bt* traits can produce 4.19 kilograms of *Bt* toxin per hectare. Data in the section of this chapter on environmental effects of GE crops indicates that *Bt* toxins are not having adverse environmental effects compared to non-*Bt* crop varieties. *Bt* toxins are proteins that are insect-specific, and they are rapidly destroyed by microbial action when the remains of GE crops decompose.

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[13] Managing Insect Pests in Organically Certified Field Corn. North Carolina State University Department of Entomology. Available at http://www.ces.ncsu.edu/plymouth/ent/neonicotinoidseedcoat.html. Accessed April 5, 2016.

Andow's (2010) critique of *Bt* eggplant disagreed with the projection that *Bt* eggplant would reduce insecticide use for small-scale farmers. He hypothesized that the *Bt* variety would not be used by smallholders and therefore there would not be a decrease in insecticide use. At the time the committee was writing its report, *Bt* eggplant has been adopted by almost 150 farmers in Bangladesh. Its effect on insecticide use remained to be seen.

> **FINDING: In all cases examined, use of *Bt* crop varieties reduced application of synthetic insecticides in those fields. In some cases, the use of *Bt* crop varieties has also been associated with reduced use of insecticides in fields with non-*Bt* varieties of the crop and other crops.**

Changes in Secondary Insect Pests Due to *Bt* Crops

The control of targeted species by *Bt* toxins sometimes provides an opportunity for populations of "secondary" insect species to increase. The secondary insect-pest populations increase because they are not susceptible to or have reduced susceptibility to the specific *Bt* trait in the crop. The insects would have been controlled by broad-spectrum insecticides that were used before the introduction of the *Bt* crop.

Bt cotton and maize are the most widely grown IR crops. The particular *Bt* proteins and their specific targets vary. Some are specific to some beetle species, others to the caterpillars of some moth species. One of the best examples of a secondary pest outbreak is in *Bt* cotton in China. In a 10-year study conducted from 1997 (when *Bt* cotton was introduced) through 2008, populations of a mirid bug (Heteroptera: Miridae), which is not affected by the *Bt* toxin in the cotton, steadily increased (Lu et al., 2010). The authors concluded that the increase was due to the mirid bugs' preference for cotton, and they were controlled with insecticide applications before the introduction of *Bt* cotton. Furthermore, mirid bug populations increased in other host crops, and these increases correlated with the extent of *Bt* cotton planting in cotton-growing regions in China. Over the 10 years of the study, there was increased damage to cotton and the other host crops, and the number of insecticide applications for mirid bug control also increased even though overall insecticide use declined. A summary assessment of the effects of secondary pests on *Bt* cotton in China (Qiao, 2015) concluded that the effects were minor in comparison with the decreases in major insect pests and insecticide use.

In the Southeast of the United States, decreased insecticide use in *Bt* cotton has been associated with an increase in cotton yield loss due to the stink bugs *Nezara viridula* and *Euschistus servus* (Zeilinger et al., 2011); in the Midwest of the United States, the western bean cutworm (*Striacosta albicosta*) became a pest after introduction of *Bt* maize. Indirect evidence indicates that the western bean cutworm became more common because it was not as affected by *Bt* toxins as the major caterpillar pests of maize, so it had an open ecological niche when the major insect pests were removed (Dorhout and Rice, 2010).

Although some secondary insect pests have increased in abundance as *Bt* crops have replaced broad-spectrum insecticides, Naranjo et al. (2008:163, 167), in a review of studies in and outside the United States on the effects of secondary insect pests, concluded that a "relatively large number of pest species that are not susceptible to the *Bt* toxins expressed in transgenic cottons affect cotton production worldwide. In general, most of these species exhibit the same pest status and continue to be managed identically in *Bt* and [non-*Bt*] cotton systems." Catarino et al. (2015) reviewed some other cases in which indirect evidence suggests an increase in secondary insect pests in *Bt* cotton and *Bt* maize. They concluded that the secondary insect pests "may not be serious enough to undermine the use of the technology, but do require further exploration so that practical and economically viable advice can be given to farmers and so that regulators are aware of potential issues and risks during a crop's approval phase."

Resistance Evolution and Resistance Management in *Bt* Crops

The evolution of target insects with resistance to *Bt* toxins has resulted in substantial economic losses for farmers of *Bt* crops. The committee heard from members of the public, researchers, and farmers that such resistance is an indication that genetic-engineering technology is not sustainable, and it reviewed evidence of the problem.

In 1996, the U.S. Environmental Protection Agency (EPA) Pesticide Program Dialogue Committee proposed that, with respect to *Bacillus thuringensis* and other environment-friendly formulations, "development of resistance would cause the potential loss of a pesticide that was in the 'public good' " (EPA, 1997). Although the EPA committee used the term *public good*, it was not clear about how to assess the term quantitatively and requested public comments (EPA, 1997). The comments submitted to EPA varied from supportive of the approach to strongly negative. In 2001, EPA clarified that it "considers protection of insect (pest) susceptibility of *Bt* to be in the 'public good'" because it "determined that development of resistant insects would constitute an adverse environmental effect" (EPA, 2001). The EPA statements reinforced the agency's early actions that required that applicants for registration of *Bt* crops develop and implement approaches for deploying the crops in ways that would delay evolution of resistance. External EPA science advisory panels endorsed the appropriate use of resistance-management strategies (EPA, 1998, 2002, 2011, 2014b).

Reports by the National Research Council in 2000 and 2010 described the scientific basis of resistance-management strategies for situations in which the pesticidal substance is produced by a plant (NRC, 2000, 2010a). Of the diverse potential strategies (Gould, 1998), the one most favored by EPA and industry is referred to as the high dose/refuge strategy. Only a short summary is provided here because details of this approach have been discussed in previous National Research Council reports. The high dose/refuge approach assumes that most alleles of genes that can confer high levels of resistance to a toxin must be homozygous (both gene copies have the resistance allele) to be able to overcome a high titer of the toxin and that such alleles are rare in an insect-pest population before use of the toxin. Furthermore, the approach requires that there be a "refuge" where insects lacking resistance can survive and preserve susceptibility alleles in the population. The refuge could be a planting of the crop itself that does not produce the toxin or of another crop or wild plant species that the insect pest feeds on but that does not contain the toxin.

The initial EPA mandates that crops have a high dose of toxin relative to insect-pest tolerances was fulfilled by *Bt* crops targeting some insect pests—for example, Colorado potato beetle (*Leptinotarsa decemlineata*), pink bollworm, and tobacco budworm (*Heliothis virescens*)—but not others—for example, cotton bollworm, fall armyworm, and western corn rootworm. For cases in which a high dose was lacking, theory clearly indicated that a much larger refuge was required to delay resistance (EPA, 2002). There is now empirical evidence that resistance has occurred less often when a high dose has been used, and there are no reported cases of resistance when a high dose and an appropriate refuge have been used together. Huang et al. (2011) pointed out that as of 2009 the three cases of field failures due to resistance were cases in which a *Bt* variety with a high dose for the target insect was not available or was not deployed. Tabashnik et al. (2013) found that in six of nine cases in which *Bt* plants met the high-dose standard there was either no decrease in target-insect susceptibility or fewer than 1 percent of individuals were resistant; however, in the 10 cases in which there was not a high dose, more than 1 percent of individuals were resistant and sometimes the toxin lost efficacy.

One problem with the industry resistance-management plans accepted by EPA is the lack of compliance with the mandated refuges by farmers (Goldberger et al., 2005; CSPI, 2009; Reisig, 2014). When refuges are planted, they are sometimes sprayed more than needed and this decreases the utility of the refuge. Other countries have also legislated refuge plans, but few have enforced them (for example, Kruger et al., 2012). Australia is an exception: There was strict maintenance of refuges for *Bt* cotton (Wilson et al., 2013).

The 2010 National Research Council report on the impacts of GE crops in the United States (NRC, 2010a) documented a few cases of resistance (defined as a genetically based change in susceptibility to a toxin) but only one in which insect-pest damage in the field increased substantially. Since then, in the United States, there have been more cases of resistance defined broadly (Tabashnik et al., 2013) and one more case of field losses in the United States due to resistance of western corn rootworm (Gassmann et al., 2014; Wangila et al., 2015). Damaging levels of resistance have also evolved in pests in other countries, for example, pink bollworm in India (Bagla, 2010; Kranthi, 2015; Kasabe, 2016), African maize stem borer (*Busseola fusca*) in South Africa (Kruger et al., 2011), and fall armyworm in Brazil (Farias et al., 2014). In all of these cases there was lack of a high dose relative to the pest's tolerance of the *Bt* toxin, a lack of a refuge for the pest, or both.

The case of pink bollworm resistance to *Bt* cotton is instructive. The first commercial cotton hybrids with one *Bt* toxin (Cry1Ac) were released in India in 2002. By 2005 in central and southern India about 93 percent of the cotton contained the *Bt* gene, and in 2008 a survey indicated 99-percent adoption, which meant that refuges were not planted (Kathage and Qaim, 2012). In 2009, Monsanto researchers confirmed field failures due to resistance in pink bollworm (Mohan et al., 2016). Cotton hybrids with two *Bt* toxins (Cry1Ac and Cry2Ab) were commercialized and replaced most single-toxin hybrids. By 2015, pink bollworm had evolved resistance to the dual-toxin cotton in the state of Gujarat and some parts of the states of Andhra Pradesh, Telangana, and Maharashtra and that caused estimated losses of 7–8 percent (Kranthi, 2015; Kasabe, 2016). Fortunately, the other cotton bollworm species (*Helicoverpa armigera*) has not evolved high enough levels of resistance to cause excess damage to the *Bt* cotton variety.

In addition to developing varieties with multiple *Bt* genes aimed at a single target insect pest, companies have also stacked *Bt* genes aimed at different pests. For example, Monsanto's SmartStax® maize variety has two *Bt* genes targeted at the European corn borer and other Lepidoptera and two other *Bt* genes aimed at the western corn rootworm. Those stacked varieties can make resistance-management approaches complicated. For example, there are two general approaches for planting a refuge: having non-*Bt* seeds planted in fields next to the *Bt* crop or having *Bt* and non-*Bt* seeds mixed in the bags of maize seed. For the European corn borer, the best approach for refuge design is having a particular percentage of fields (or blocks of rows) planted in non-*Bt* seed to serve as refuges. For European corn borer, seed mixtures could be problematic because the insect larvae could move between *Bt* and non-*Bt* plants in the seed mixture and receive an intermediate dose of the toxin (Mallet and Porter, 1992; Gould, 1998). For corn earworm, a problem sometimes attributed to the use of seed mixtures is that the non-*Bt* plants can be pollinated by the *Bt* maize in the mixture. For corn rootworm, a seed mixture or a block-to-block mixture should have similar effects. The result of that is that one-half or more of the kernels in the ears have *Bt* toxin, so when the corn earworm feeds on the ears of the "refuge" maize, it is exposed to *Bt* toxin, negating the utility of the refuge (Yang et al., 2014). It is important to note that with corn earworm, the *Bt* toxin levels do not result in a high dose, so the small refuges are never expected to be effective unless the resistance trait is genetically recessive (Gould, 1998; Brévault et al., 2015). It is assumed that for western corn rootworm a seed mixture of *Bt* and non-*Bt* seed is reasonable because the soil-dwelling larvae do not typically move between plants. In that case, the varieties available in 2015 did not produce a high dose, so the utility of the small current refuge would be limited with or without movement of larvae unless, again, the resistance trait was recessive. In an article (Andow et al., 2016), a group of 10 entomologists and economists who work on maize production concluded that "farmers should be encouraged to move away from a mentality of 'what trait do I use' to a multifaceted pest management approach. This integrated approach should start as soon as a new technology is commercialized, so that it can be more effectively stewarded by reducing the rate of resistance evolution, especially for traits with less than a high-dose." The committee agrees that this would be an appropriate approach but that implementation would require carefully constructed, long-term incentives for farmers; farmers currently have little choice but to look for the next trait to come along. A publication by Badran et al. (2016) demonstrated a new technology that might be able to more quickly generate new *Bt* toxins and thus provide that next hoped-for new trait; however, at the time the committee was writing its report, it was only a proof of concept.

As described in Box 4-2, *Bt* crops have caused the European corn borer population to decline to the point where they are well below economic thresholds, so it often is not economically favorable for farmers to grow maize with the *Bt* toxins that are aimed primarily at the corn borers (Hutchison et al., 2010; Bohnenblust et al., 2014). The field-to-field (or blocks of rows) planting of *Bt* and non-*Bt* maize appears to have mitigated resistance evolution in the European corn borer, but a seed mix may compromise the refuge (NRC, 2010a; Carrière et al., 2016). This situation is suboptimal because, even though there are fewer corn borers and little damage, the same percentage of corn borers are being exposed to the *Bt* toxins no matter what their density, and unless total numbers of the pests in a region are below a million, it is the percentage exposure and not the number exposed that is expected to have the greatest effect on the rate at which resistance genes increase in frequency. For European corn borer, even in Wisconsin where, only about 3 percent of all maize plants are infested, the population of these insects is estimated at over 3 billion. It is not now possible to purchase maize with *Bt* toxins aimed at western corn rootworm but without those aimed at European corn borer.

As trait stacking becomes more common and involves both insect pests and pathogens, providing optimal combinations of traits and refuges will become more important. It is difficult for seed providers to maintain inventories of multiple varieties that provide farmers with the ability to match traits with their specific needs, but that is an issue that should be addressed in order to slow the evolution of resistance.

As noted above, many countries do not enforce refuge guidelines. Another problem for developing countries is that the *Bt* toxins incorporated into crops as of 2015 have been designed mostly for insect pests of the United States. The major insect pests in developing counties are often different from those in the United States, and the *Bt* toxins in the crops might be only marginally useful for pests in those countries and more likely to cause evolution of resistance. The cases of the African maize stem borer (Kruger et al., 2011) and some armyworm species in Brazil (Bernardi et al., 2014) are examples of how *Bt* toxins developed for U.S. insect pests have suboptimal effects on pests in developing countries and resulted in evolution of resistance.

FINDING: The high dose/refuge strategy for delaying evolution of resistance to *Bt* toxins appears to have been successful, but deployment of crops with intermediate levels of *Bt* toxins and small refuges has sometimes resulted in the evolution of resistance in insect pests that erodes the benefits of the *Bt* crops.

FINDING: The widespread deployment of crops with *Bt* toxins has decreased some insect-pest populations to the point where it is economically realistic to increase plantings of crop varieties without a *Bt* toxin that targets these pests. Planting varieties without *Bt* under those circumstances would delay evolution of resistance further.

RECOMMENDATION: Given the theoretical and empirical evidence supporting the use of the high dose/refuge strategy 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.

RECOMMENDATION: Seed producers should be encouraged to provide farmers with high-yielding crop varieties that only have the pest resistance traits that are economically and evolutionarily appropriate for their region and farming situation.

EFFECTS RELATED TO THE USE OF HERBICIDE-RESISTANT CROPS

The committee 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. As in the section on *Bt* crops, it relied in part on previous reviews but went beyond that in examining specific studies in order to provide the reader with the strengths and weaknesses of studies used to support specific claims about HR crops.

Yield Effects of Genetically Engineered Herbicide Resistance

As of 2015, GE herbicide resistance had been incorporated into soybean, maize, cotton, canola, sugar beet (*Beta vulgaris*), and alfalfa (*Medicago sativa*). With the exception of alfalfa, for which GE varieties are resistant only to glyphosate, varieties of those crops with GE resistance to other herbicides in addition to glyphosate had been developed (see Table 3-1), but not all were commercially available. In the first 20 years of GE crop production, glyphosate resistance was the predominant GE herbicide-resistant trait used by farmers.

Herbicide-Resistant Soybean

Areal et al. (2013) found no difference in yield between HR soybean and non-GE soybean on the basis of a meta-analysis of data collected in the United States, Canada, Argentina, and Romania in 1996–2003. Fernandez-Cornejo et al. (2014) found mixed results in their summary of studies on HR soybean in the United States published in 1995–2004. Three studies reported an increase in yield, one reported a small increase, one reported a small decrease, and four reported no difference.

In a field experiment in Brazil in the three crops seasons of 2007–2010, Bärwald Bohm et al. (2014) found that glyphosate-resistant soybean treated twice with glyphosate, 28 and 56 days after planting, yielded the same as the same glyphosate-resistant variety that was treated only once or that was hand-weeded instead of being sprayed with glyphosate. These yields also did not differ from those on a plot of non-HR isogenic soybean that was hand-weeded.

Another experiment in Brazil examined yield of glyphosate-resistant soybean at six locations in the growing seasons of 2003–2004, 2004–2005, and 2005–2006 (Hungria et al., 2014). Glyphosate-resistant soybean treated with glyphosate was compared with four other scenarios: the same HR variety treated with other herbicides typically used with non-HR soybean, the non-HR parent line of the HR soybean treated with other herbicides typically used with non-HR soybean, the HR soybean with hand-weeding, and the non-HR parent line of the HR soybean with hand-weeding. No difference in yield was found between the plots with HR soybean (treated with glyphosate, treated with other herbicides, and hand-weeded) and those with non-HR soybean in five of the six locations.[14] When the plots with HR soybean treated with glyphosate were compared with the plots with the HR soybean treated with other herbicides, yields for the HR soybean treated with glyphosate in four of the locations were greater. When HR soybean treated with glyphosate was compared with the non-HR parent line of the HR soybean treated with other herbicides, the yields for the HR soybean were greater in three of the locations.

In field experiments in Iowa conducted in 2007 and 2008, Owen et al. (2010) found that HR varieties (three resistant to glyphosate and three resistant to the herbicide glufosinate) had greater yields than three non-HR varieties. The result was the same when none of the varieties was treated with post-emergence herbicides or when the glyphosate-resistant varieties were treated with glyphosate, the glufosinate-resistant varieties were treated with glufosinate, and the non-HR varieties were treated with post-emergence herbicides. No differences in yield were observed among the HR varieties over the 2 years or in the experiments' three sites. In a different experiment in Iowa in 2010 there were no differences in the mean yield between three populations of glyphosate-resistant soybean and three non-HR counterpart populations planted at four locations, with one exception: at one location, one of the glyphosate-resistant populations had a mean yield 1.6 percent greater than its counterpart (De Vries and Fehr, 2011).

Field experiments in two locations in Missouri during the summers of 2009 and 2010 compared different combinations of pre-emergence and post-emergence herbicide programs in non-GE soybean, glyphosate-resistant soybean, and glufosinate-resistant soybean (Rosenbaum et al., 2013). Averaged among locations and treatments, glufosinate-resistant soybean had the greatest yields (2,688 kilograms/hectare), followed by glyphosate-resistant soybean (2,550 kilograms/hectare) and non-GE soybean (2,013 kilograms/hectare). In control plots, to which no herbicides were applied, yields were similar in all three varieties; this indicated that glufosinate and glyphosate herbicide programs with GE soybean provided better control of competing weeds than did herbicide programs with non-GE soybean.

Soybean with GE resistance to the imidazolinone class of herbicides was first approved for commercial production in 2010 in Brazil. In 2007–2008, Hungria and colleagues tested GE imidazolinone-resistant soybean against a non-HR isoline. HR soybean treated with an imidazolinone herbicide

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[14] The sixth location experienced drought, and yield data were collected only for one growing season.

was compared with HR soybean treated with other post-emergence herbicides and with the non-HR isoline treated with other post-emergence herbicides. No differences in yield were observed among the three treatments or over time (Hungria et al., 2015).

Gurian-Sherman (2009) also reported little or no effect on yield in a review of studies of HR soybean conducted in 1999–2006 in the United States. He raised the issue of yield drag, which was also discussed in the 2010 National Research Council report on GE crops, and yield lag (NRC, 2010a).[15] Gurian-Sherman and the National Research Council report looked at the same studies from the early 2000s[16] and found evidence of yield drag and yield lag. However, more recent studies, such as those reviewed above, demonstrate that yield drag and yield lag appear to have been overcome in HR soybean because the yields of HR soybean are the same as or more than the yields of non-HR soybean. As with some of the results described for *Bt* crops, Owen et al. (2010) hypothesized that the lower yield observed in a non-GE soybean (not treated with post-emergence herbicides) than in glyphosate-resistant soybean and glufosinate-resistant soybean (also not treated after emergence with their counterpart herbicides) in a 2007–2008 experiment could be due to yield lag in the genetic potential of the non-GE variety.

Herbicide-Resistant Maize

Thelen and Penner (2007) compared the yields of glyphosate-resistant maize treated with glyphosate and glyphosate-resistant maize treated with other herbicides. Three field sites in different counties in Michigan were monitored for 5 years (2002–2006). At two of the sites, there was no difference in the 5-year average yield between fields treated with glyphosate and fields treated with other herbicides. At the third site, the glyphosate-treated

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[15] "Yield lag is a reduction in yield resulting from the development time of cultivars with novel traits (in this case, glyphosate resistance and Bt). Because of the delay between the beginning of the development of a cultivar with a novel trait and its commercialization, the germplasm that is used has lower yield potential than the newer germplasm used in cultivars and hybrids developed in the interim. Consequently, the cultivars with novel traits have a tendency to initially yield lower than new elite cultivars without the novel traits. Over time, the yield lag usually disappears.

"Yield drag is a reduction in yield potential owing to the insertion or positional effect of a gene (along with cluster genes or promoters). This has been a common occurrence throughout the history of plant breeding when inserting different traits (e.g., quality, pest resistance, and quality characteristics). Frequently, the yield drag is eliminated over time as further cultivar development with the trait occurs." (NRC, 2010a:142)

[16] The National Research Council report (2010a) reviewed the same two reports reviewed in Gurian-Sherman (2009) and several others.

maize, averaged over 5 years, had a yield advantage over glyphosate-resistant maize treated with other herbicides.

Field studies in Illinois in 1999 and 2000 compared four kinds of maize hybrids suited to the growing region (Nolte and Young, 2002). One hybrid was non-GE, one was not genetically engineered but was resistant to the imidazolinone class of herbicides, one was genetically engineered with resistance to glyphosate, and one was genetically engineered with resistance to glufosinate. There was no difference in yield among the non-GE hybrid, the non-GE imidazolinone-resistant hybrid, and the GE glufosinate-resistant hybrid. In the first year, yield for the GE glyphosate-resistant hybrid was lower; in the second year, its yield was greater than that of the other hybrids. The authors hypothesized that the glyphosate-resistant hybrid was more sensitive to temperature and moisture stress and that its yield responded more to stressful growing conditions in the first year and more to ideal growing conditions in the second year.

Almost all the data on yield effects of HR maize come from North America. However, Gonzales et al. (2009) collected data from six provinces in the Philippines and found that three provinces reported a yield advantage (but with no statistical information) from HR maize when compared with average yield of non-GE hybrids in the wet season of 2007–2008. Three other provinces reported a yield disadvantage. In the dry season of 2007–2008, five provinces reported a yield advantage; the average yield in two other provinces was nearly equivalent between HR and non-GE maize. Two years later, in the wet season of 2010, Afidchao et al. (2014) reported that HR maize yielded the same as non-GE maize in the Isabela province of the Philippines.

Herbicide-Resistant Cotton

Most cotton varieties produced since 2005 in the United States have HR and IR traits. India, China, and Pakistan—the other large producers of cotton—grow *Bt* varieties. The wide adoption of *Bt*-HR varieties and *Bt*-only varieties means that little recent research has been devoted to comparing the yields of HR and non-HR cotton.

Herbicide-Resistant Canola

GE canola with resistance to glyphosate or glufosinate is in commercial production. In a study conducted over 3 years in Great Britain, GE glufosinate-resistant canola (oilseed rape) was found to be less invasive and persistent than the non-GE comparators (Crawley et al., 1993). Stringam et al. (2003) reviewed the introduction of GE varieties in Canada, using data from variety trials that compared GE and non-GE varieties and yield estimates from producers. The data did include statistical comparisons. They found yield increases of as much as 39 percent for GE varieties, but most differences were smaller. Harker et al. (2000) reported that yields were greater when the GE glyphosate-resistant or glufosinate-resistant varieties were treated with glyphosate or glufosinate, respectively, compared with treatment with standard herbicides used in canola. Those yield increases were as much as 38 percent greater, which they attributed to improved weed control in some circumstances but also to higher potential yield in the germplasm of the HR varieties. In field studies conducted throughout Canada under different environmental conditions, yield of the GE and non-GE varieties was similar (Clayton et al., 2004). Beckie et al. (2011) reported that the rapid adoption of GE canola is due to better weed control and to greater yields and economic returns.

Herbicide-Resistant Sugar Beet

Kniss et al. (2004) compared yield of two non-GE and two GE glyphosate-resistant sugar beet varieties in studies conducted in Nebraska in 2001 and 2002 (before HR sugar beets were commercially sold). Although not reported to be isolines, the varieties were paired for evaluation on the basis of a high degree of shared genetic backgrounds. The non-GE varieties were treated with herbicides that would typically be used for weed control, but glyphosate was the only herbicide applied to the resistant varieties. In one case, the glyphosate-resistant variety (Beta 4546RR) produced greater sucrose content than the nonresistant variety (Beta 4546). The authors concluded that the difference was due to reduced herbicide injury and better weed control. In the other case, even though there were less crop injury and increased weed control, the GE sugar beet variety (HM 1640RR) did not have greater sucrose content than its nonresistant HM variety counterpart. The authors proposed that the difference in response was due to the Beta varieties' greater genetic similarity than that of the HM varieties. Sucrose production is not controlled by a single gene, so the difference between the two sets of varieties would account for differences in sucrose concentration rather than in the resistance trait. The resistant Beta variety produced a greater yield and gross sucrose production than the nonresistant Beta variety in all but one treatment. The yield results of the HM varieties were less definitive, with few differences in yield or gross sucrose production. The authors concluded that planting a glyphosate-resistant variety versus a non–glyphosate-resistant variety will not necessarily return greater profits but that it is important to choose a variety that is high-yielding and locally adapted.

Kniss (2010) compared yield of non-GE and glyphosate-resistant sugar beet on a field scale in Wyoming in 2007, the first year of commercial production. The fields were chosen on the basis of the criteria that paired fields with glyphosate-resistant sugar beets or non-GE sugar beets were managed by the same grower and had similar slopes, soil types, irrigation, and production histories. The growers controlled management decisions on both fields. Tillage was lower in the glyphosate-resistant sugar beet than in the non-GE sugar beet fields. Sugar content was similar in the resistant and nonresistant sugar beets, but yield was greater in the glyphosate-resistant sugar beet fields, so the gross sucrose production was greater. The study was conducted in only one year because in 2008 farmer adoption of the glyphosate-resistant varieties was so great that non-GE sugar beet fields were not available to repeat the study.

Other studies have compared the yield of glyphosate-resistant varieties after applications of glyphosate versus commonly used herbicides in the United States (Guza et al., 2002; Wilson et al., 2002; Armstrong and Sprague, 2010) and in Germany and Poland (Nichterlein et al., 2013). In the studies conducted in the United States, there was some variation among sites in weed control and yield. In Idaho, weed control and yield were comparable in plants treated with glyphosate and with the herbicides typically used in sugar beet production (Guza et al., 2002). In Nebraska, weed control was similar between the glyphosate treatments and the treatments with commonly used herbicides, but sucrose yield was reduced with the treatments with commonly used herbicides (Wilson et al., 2002). In Michigan, glyphosate provided better weed control than commonly used herbicides, but yield in kilograms of sugar was similar (Armstrong and Sprague, 2010). In the studies conducted in Germany and Poland of glyphosate-resistant sugar beet treated with glyphosate versus treatment with herbicides typically used in sugar beet production, yields of the former were greater only in some trials (Nichterlein et al., 2013). However, fewer herbicide applications were required, and there was a reduction in kilograms of active ingredients applied. Therefore, the authors concluded that growing glyphosate-resistant sugar beet would lead to a reduction in herbicide use.

Wilson et al. (2002) and Kemp et al. (2009) included glufosinate-resistant varieties in their studies. Weed control and yields were similar for all treatments. At the writing of this report, no glufosinate-resistant varieties were in commercial production.

Herbicide-Resistant Alfalfa

Glyphosate-resistant alfalfa has not been grown for as many years as the other resistant crops, so fewer studies of it have been published. In addition, alfalfa is a perennial crop, so evaluation of its field performance will require more years than for that of the annual crops discussed previously. Data on the yield of glyphosate-resistant alfalfa in peer-reviewed publications are sparse. One study compared yield, weed biomass, and forage quality of glyphosate-resistant alfalfa and non-GE alfalfa (Sheaffer et al., 2007). In the year of seeding and the following year, the two systems were similar in yield and forage quality.

> **FINDING: HR crops contribute to greater yield where weed control is improved because of the specific herbicides that can be used in conjunction with the HR crop.**

Changes in Herbicide Use Due to Herbicide-Resistant Crops

Findings on the effect of glyphosate-resistant crops on the amount of herbicide applied per hectare of crop have been diverse. There is doubt about the utility of simply measuring the amount of herbicide without reference to the environmental and health effects per kilogram of each herbicide used. The committee first presents the reviews of data on amount of herbicide used and then examines the relevance of these data.

The assessment by Klümper and Qaim (2014) concluded that the amount of herbicide applied to HR soybean, maize, and cotton compared to their non-GE counterparts was essentially unchanged from non-HR counterparts (-0.6 percent; n=13). Barfoot and Brookes (2014) concluded that, on an overall global level for the period between 1996 and 2012, the volume of herbicide active ingredients applied decreased by 0.2 percent (soybean) to 16.7 percent (canola) and that only application to sugar beet increased (25.6 percent). Qaim and Traxler (2005) found that herbicide application rates for HR soybean in Argentina doubled during 1996–2001. Here the growers substituted glyphosate for herbicides in higher toxicity classes (Nelson and Bullock, 2003; Cerdeira and Duke, 2006).

In the United States, Fernandez-Cornejo et al. (2014) found that herbicide use on maize in terms of a.i. had decreased from about 2.9 kilograms/hectare in the early years of HR maize adoption to less than 2.2 kilograms/hectare in 2002. Herbicide use increased slightly from 2002 to 2010 (Figure 4-8). For soybean and cotton, there were initial decreases in a.i. per hectare, but amounts in 2008 (soybean) and 2010 (cotton) were greater than amounts in 1995 (Fernandez-Cornejo et al., 2014). USDA data were 1.6 kilograms/hectare for soybean in 2012 (USDA–NASS, 2013) and 2.1 kilograms/hectare for maize in 2014 (USDA–NASS, 2015). Statistical significance was not reported.

Benbrook (2012) also assessed USDA data and concluded (without a statistical analysis) that herbicide application rates in kilograms of a.i. per hectare per year were greater in 2006–2010 than in 1996 for soybean and cotton (soybean, 1.3 kilograms/hectare in 1996 and 1.6 kilograms/hectare in 2006; cotton, 2.1 kilograms/hectare in 1996 and 3.0 kilograms/hectare in

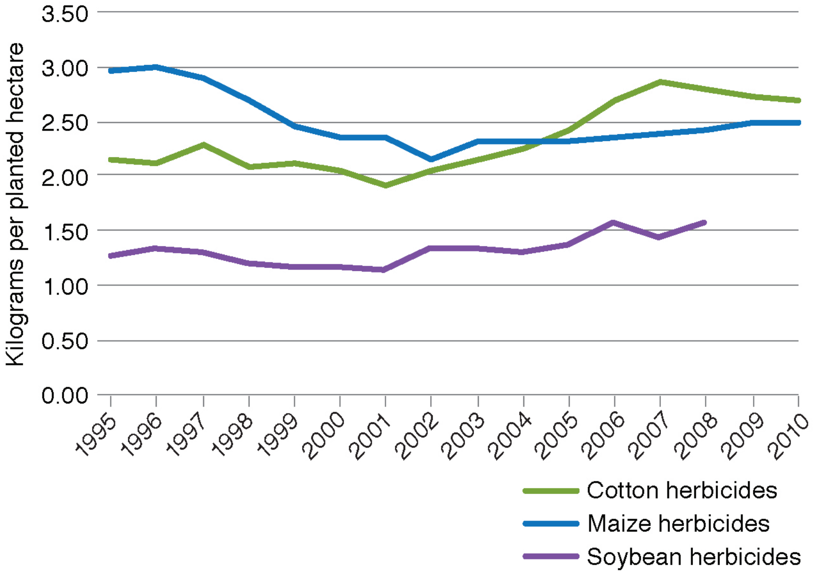

FIGURE 4-8 Herbicide use in cotton, maize, and soybean in the United States, 1995–2010.
SOURCE: Fernandez-Cornejo et al. (2014).

2010) but less for maize (3.0 kilograms/hectare in 1996 and 2.5 kilograms/hectare in 2010). Benbrook pointed out that data on kilograms per hectare may be misleading because some herbicides are effective at about 1.0 kilograms/hectare and others at less than 0.1 kilograms/hectare. An overall decrease or increase in kilograms per hectare could simply reflect a change in use of high-efficacy and low-efficacy herbicides and not necessarily reflect increased desirability from a human-health or environmental perspective. To address that problem, some researchers, including Barfoot and Brookes (2014), use an environmental impact quotient (EIQ) for evaluating herbicides and insecticides (Kovach et al., 1992). However, EIQ has not been found to be a substantially better indicator of environmental impact than kilograms per hectare (Kniss and Coburn, 2015). Kniss and Coburn (2015) argued convincingly that neither kilograms per hectare nor EIQ is a useful metric and that only careful case-by-case evaluation of the environmental and health impacts of each herbicide will yield useful assessments. They recommended use of the EPA risk-quotient approach. Mamy et al. (2010) provided a comparative environmental risk assessment of glyphosate and other herbicides. Nelson and Bullock (2003) presented an approach for measuring a proxy for human toxicity risk per application of an herbicide.

Assessing the relative effects of diverse herbicides can be challenging, but it is clear that simply determining if the total kilograms/hectare of herbicide used per year has gone up or down is not useful for assessing human or environmental risks.

> **FINDING: The use of HR crops sometimes initially correlated with decreases in total amount of herbicide applied per hectare of crop per year, but the decreases have not generally been sustained. However, such simple determination of whether total kilograms of herbicide used per hectare per year has gone up or down is not useful for assessing changes in human or environmental risks.**
>
> **RECOMMENDATION: Researchers should be discouraged from publishing data that simply compares total kilograms of herbicide used per hectare per year because such data can mislead readers.**

Changes in Weed Species Densities Due to Herbicide-Resistant Crops

Once the HR crops are introduced and used continuously, the repeated applications of a single herbicide with no other weed-management techniques leads to increases in weed species that are not sensitive to the herbicide or that respond to other changes in production practices. Glyphosate controls many monocot and dicot weeds, but it does not control all weed species equally. Some of the weed species that are tolerant to glyphosate have become more problematic in glyphosate-resistant crops. In the United States, a survey of 12 weed scientists in 11 states in 2006 indicated that several weed species were increasing in glyphosate-resistant crops (Culpepper, 2006); they included morning glories (*Ipomoea* spp.), dayflowers (*Commelina* spp.), and sedges (*Cyperus* spp.). One weed species that decreased in density within crop fields was common milkweed (*Asclepias syriaca*) (Hartzler, 2010). Other shifts in weed species abundance were occurring in U.S. crop production areas, but they were attributed to time of application of the herbicide rather than to overall weed sensitivity to the herbicide. Owen (2008) and Johnson et al. (2009) reviewed the literature and found some strong shifts to weeds that are hard to manage, such as giant ragweed (*Ambrosia trifida*), horseweed (*Conyza canadensis*), common and narrowleaf lambsquarters (*Chenopodium album*), morning glories, and shattercane (*Sorghum bicolor ssp. X. drummondii*). Some of the changes in weed species at that time could also have been associated with the increase in use of no-till and reduced-till crop production practices.

Now that crops with stacked herbicide-resistant traits such as 2,4-D and glyphosate are being commercialized, it is possible that different weeds will increase or decrease, but such changes may not be problematic for production agriculture unless previously minor weed species pose severe problems. Furthermore, as discussed below (see section "Herbicide-Resistant Crops and Weed Biodiversity"), the increased use of glyphosate does not appear to have affected the general diversity of weeds in cropping systems (Gulden et al., 2010; Schwartz et al., 2015).

> **FINDING: Both for insect pests and weeds, there is evidence that some species have increased in abundance as IR and HR crops have become widely planted. However, in only a few cases have the increases posed an agronomic problem.**

Resistance Evolution and Resistance Management for Herbicide-Resistant Crops

When glyphosate-resistant crops were commercialized in the United States, neither USDA nor EPA required resistance-management plans to delay the evolution of glyphosate-resistant weeds. The repeated use of glyphosate on glyphosate-resistant crops, which were adopted rapidly and widely, quickly led to selection for weeds with evolved resistance to glyphosate (Box 4-3). In 2000, marestail (*Conyza canadensis* L.) was the first glyphosate-resistant weed to be confirmed in an HR cropping system (VanGessel, 2001). The resistant marestail was selected in glyphosate-resistant soybean within 3 years of the use of glyphosate alone for weed management. Glyphosate was used to suppress weeds in crops for many years before the advent of GE crops, typically by spraying before a crop plant emerged from the ground or after harvest. It is still used in crops without GE herbicide resistance. However, at least 16 of the 35 reported glyphosate-resistant weed species identified (Heap, 2016) evolved in fields where HR crops were grown. Glyphosate-resistant weeds have been identified in Argentina, Australia, Bolivia, Brazil, Canada, Chile, China, Colombia, Costa Rica, the Czech Republic, Greece, France, Indonesia, Israel, Italy, Japan, Malaysia, Mexico, New Zealand, Paraguay, Poland, Portugal, South Africa, Spain, Switzerland, Taiwan, the United States, and Venezuela (Heap, 2016). The National Research Council held a workshop to assess the resistance problem and potential solutions (NRC, 2012). A study conducted by the USDA Economic Research Service (Livingston et al., 2015) estimated the reduction in total returns in maize and soybean in the United States due to the cost of glyphosate-resistant weeds at $165/hectare and $56/hectare, respectively. Livingston and colleagues (2015:i) concluded that "managing glyphosate resistance is more cost effective than ignoring it, and after about 2 years, the cumulative impact of the returns received is higher when managing instead of ignoring resistance." The committee could not find cost estimates for other countries. However, Binimelis

BOX 4-3
Evolution of Glyphosate-Resistant Palmer amaranth in Glyphosate-Resistant Cotton

Results of surveys conducted by the U.S. Southern Society of Weed Science from 1974 to 1995 indicated that Palmer amaranth (*Amaranthus palmeri*) was not a common weed or a weed that was difficult to control in cotton, although *Amaranthus* species were ranked sixth in the 1974 survey and fourth in the 1995 survey (Webster and Coble, 1997). The authors of the survey noted that Palmer amaranth ranked number one in weed species that could be expected to increase in difficulty to control and become an important weed problem. Further, they warned of herbicide resistance becoming a greater problem. Palmer amaranth with resistance to dinitroaniline herbicides already was widespread in South Carolina. They also noted that reduced tillage, removal of herbicides from the system, and the use of herbicide-resistant (HR) crops would change the weed populations present.

Commercial production of glyphosate-resistant cotton began in 1997. Initially, glyphosate-resistant cotton seemed to lead to an increase in the area of monoculture cotton and conservation tillage, the reduction in non-glyphosate and pre-emergence herbicides (Culpepper et al., 2006). Monoculture cropping and repeated use of the same herbicide are a common link to the evolution of herbicide-resistant weeds.

Glyphosate-resistant Palmer amaranth was found in a glyphosate-resistant cotton field in 2004 (Culpepper et al., 2006). Since 2004, glyphosate-resistant Palmer amaranth has spread throughout regions where glyphosate-resistant crops are grown and occurs in glyphosate-resistant cotton, maize, and soybean (Nichols et al., 2009; Ward et al., 2013). In 2009, Palmer amaranth was ranked as the number one weed species in cotton production in the southern United States, mostly due to its resistance to glyphosate (Webster and Nichols, 2012). In 2016, glyphosate-resistant Palmer amaranth was reported in 25 U.S. states and in Brazil (Heap, 2016).

Glyphosate-resistant Palmer amaranth transformed weed management in HR cotton production in the southern United States. In response to the evolution and spread of glyphosate-resistant Palmer amaranth, cotton growers in Georgia reported increased use of non-glyphosate herbicides, including those that must be incorporated into the soil; increased tillage (required for incorporation of some herbicides), mechanical weed control, and deep tillage to bury Palmer amaranth seed to prevent emergence; and hand-weeding, which increased from 3 to 52 percent of the cotton hectares (Sosnoskie and Culpepper, 2014).

HR cotton varieties with glufosinate, dicamba, or 2,4-D resistance traits have been deregulated and commercialized in the United States (USDA–APHIS, 2011, 2015a,b). The traits have been stacked so that herbicide mixtures can be applied for weed control and could control weeds that have evolved resistance to glyphosate. In some cases, glyphosate resistance is included as one of the stacked traits. It remains to be seen whether effective resistance management will be implemented with these traits (Inman et al., 2016).

et al. (2009) quoted sources in Argentina to the effect that controlling glyphosate-resistant Johnsongrass (*Sorghum halepense*) increased soybean production cost by 19 percent and doubled herbicide costs.

Powles (2008) pointed out that in many regions in the world glyphosate resistance has not yet evolved and that some widely planted crops, such as wheat and rice, do not yet have commercially available glyphosate-resistant varieties. Powles made a strong case for learning from the problems in maize and soybean that continuous use of glyphosate will not be beneficial in the long term.

There is disagreement in the weed-science research community about the benefit of stacking multiple HR traits and spraying multiple herbicides for resistance management (Wright et al., 2010; Egan et al., 2011; Mortensen et al., 2012). Evolutionary theory suggests that combinations of herbicides in tank mixes are expected to substantially delay resistance compared to use of a single herbicide only when weeds that are resistant to one herbicide are still killed by the second herbicide in the tank mix (Tabashnik, 1989; Gould, 1995; Neve et al., 2014). The stacked HR traits that had been or were being commercialized when the committee wrote its report will provide resistance to various combinations of glyphosate, glufosinate, 2,4-D, and dicamba. Those herbicides have different sites of action, so crops with stacked HR traits could reduce specific selection pressure from glyphosate. However, that would not be the case for all weed species because some weeds are susceptible to only one herbicide in mixed herbicide applications. For example, glyphosate has activity on both monocots and dicots whereas 2,4-D and dicamba control only dicots; therefore, monocots exposed to a tank mix of glyphosate and 2,4-D or dicamba are functionally being controlled only with glyphosate.

Evans et al. (2016:74) analyzed resistance to glyphosate in the major weed common waterhemp (*Amaranthus tuberculatus*) on 105 farms in Illinois and determined that combined spraying of herbicides that have different sites of action to that weed (that is, tank mixes) reduced the likelihood of evolution of glyphosate-resistant waterhemp on a farm. From their large-scale study, the authors concluded that "although measures such as herbicide mixing may delay the occurrence of [resistance in weeds to glyphosate] or other HR weed traits, they are unlikely to prevent [it]."

There is uncertainty regarding the best approaches for using single and multiple herbicides to delay resistance evolution in weeds. Spraying mixtures of herbicides could be useful, but theoretical and empirical evidence for the utility of this approach is weak. More research at the farm level and in experimental plots and biochemical, genomic, and population genetic research are needed to decrease the uncertainty and develop better resistance-management approaches. It is generally recognized that the less often a control measure is used, the longer it takes for resistance to evolve, and a number of integrated weed-management approaches could decrease the need for heavy reliance on herbicides, but they are not widely practiced in large-scale cropping systems in the United States (Wiggins et al., 2015). The use of judicious tillage, a key component of integrated weed management (Mortensen et al., 2012), can be highly effective in suppressing herbicide-resistant weeds in some cropping systems (Kirkegaard et al., 2014). Tillage once every 5 years within no-till and reduced-till cropping systems can be done without detrimental effects on grain yield or soil properties (Wortmann et al., 2010; Giller et al., 2015). Other aspects of integrated weed management, such as crop rotation and use of cover crops, which in some areas of the United States are promoted with economic incentives to reduce nitrate leaching (Mortensen et al., 2012), fit well with approaches to conservation tillage. In general, integrated weed management requires a detailed understanding of the weed-community ecology in a specific area. Without availability of knowledgeable extension agents to assist farmers in implementing diverse approaches to suppress weed populations, it will be difficult for farmers to move away from intensive use of herbicides.

EPA's 2014 document on the registration of the herbicide Enlist Duo™, which contains a mixture of glyphosate and 2,4-D and is targeted at GE crops that are resistant to both, includes a requirement for the registering company to develop a resistance-management plan (EPA, 2014a). On the basis of the committee's review of the theoretical and empirical literature, there is no scientific consensus on the best practices for delaying resistance simply through use of mixtures of herbicides. There is an obvious need for weed management that includes approaches other than continuous use of herbicides.

FINDING: Weed resistance to glyphosate is a problem and could be delayed by the use of resistance-management tactics especially in cropping systems and regions where weeds have not yet been exposed to continuous glyphosate applications.

RECOMMENDATION: To delay evolution of resistance to herbicides in places where GE crops with multiple HR traits are grown, integrated weed-management approaches beyond simply spraying mixtures of herbicides are needed. This will require effective extension programs and incentives for farmers.

RECOMMENDATION: 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 resistance-management strategies.

YIELD EFFECTS OF GENETICALLY ENGINEERED HERBICIDE AND INSECT RESISTANCE

As of 2015, GE varieties of soybean, maize, and cotton with both HR and IR traits were available in some countries. Most varieties had only one HR trait, which was most often glyphosate resistance. Many varieties contained more than one *Bt* toxin to target different insect pests.

Bt-HR soybean was planted for commercial production in Brazil, Argentina, Paraguay, and Uruguay starting in 2013 (Unglesbee, 2014). In two environmental studies, Beltramin da Fonseca et al. (2013) found that number of pods per plant and yield for *Bt*-HR soybean were greater than those of non–*Bt*-HR soybean.

Nolan and Santos (2012) found that maize with GE traits of *Bt* targeting European corn borer and herbicide resistance had a yield advantage of 501 kilograms/hectare over a non-GE variety. The advantage for herbicide resistance with *Bt* targeting corn rootworm was even greater (921 kilograms/hectare). All three traits combined provided a yield advantage of 927 kilograms/hectare. In 2010, Afidchao et al. (2014) reported that *Bt*-HR maize yielded the same as non-GE maize in the Isabela province of the Philippines.

Bauer et al. (2006) compared two *Bt*-HR cotton varieties to their non-GE parents in field experiments planted on three dates in spring 2000 and 2001 in South Carolina. Lint yield was not different between the transgenic lines and the parent lines regardless of planting date.

ENVIRONMENTAL EFFECTS OF GENETICALLY ENGINEERED CROPS

Diverse views have been expressed about the possibility that GE crops have adverse environmental effects. They include declines in natural enemies of insect pests, in honey bees (*Apis* spp.), and in monarch butterflies (*Danaus plexippus*) and in plant and insect biodiversity in general. At a landscape level, there is concern that GE crops contaminate other crops and wild relatives through gene flow. There is also concern that GE crops have resulted in more use of monoculture over space and time because, with protection from insect pests and availability of more effective herbicides, it becomes more profitable to grow a single crop that has the highest economic return, even if that means ignoring crop-rotation practices. It has also been suggested that GE crops are causing more fertilizer and herbicide runoff into waterways. In this section, the committee examines the evidence regarding those concerns.

Effects of Genetically Engineered Crops on Biodiversity on Farms

With regards to biodiversity on the farm, the committee looked for changes in the abundance and diversity of insects and weeds in GE cropping systems and changes in the diversity of types of crops planted and the genetic diversity in each crop species.

Bt Crops and Arthropod Biodiversity

The National Research Council report on the impact of GE crops on farm sustainability in the United States noted that generalist predators tended to be unchanged or were more abundant where *Bt* crops replaced non-*Bt* crops, especially when the non-*Bt* crops were sprayed with synthetic insecticides (NRC, 2010a). However, there were no data for assessing whether that translated into more effective biological control on a farm scale. More recently, Lu et al. (2012) reported a widespread and large increase in generalist predators (ladybirds, lacewings, and spiders) in China in association with the adoption of *Bt* cotton. That increase in generalist predators spilled over on to non-*Bt* crops (maize, peanut, and soybean) and resulted in enhanced biological control of aphid pests. It is important to note that the reported effect arises because of a contrast between heavy insecticide use (pyrethroids and organophosphates) in nonorganic, non-*Bt* cotton and substantially reduced insecticide use in *Bt* cotton. The committee could find no other similar studies since publication of those results.

It is expected that when an insect-pest population declines dramatically because of *Bt* crops, as in the case of European corn borer in the United States, there will be an accompanying decline in any host-specific parasitoid or pathogen of the pest, and the parasitoid or pathogen could even become locally extinct (Lundgren et al., 2009). Under such conditions, if the pest later evolves resistance to the *Bt* toxin, it could increase in density because it would lack natural control. The committee was unable to find any quantitative studies that tested for reductions in pest-specific natural enemies.

Beyond examining natural enemies of crop insect pests, the National Research Council report on GE crop impacts examined effects of *Bt* crops on general arthropod biodiversity on farms (NRC, 2010a). In comparisons between *Bt* varieties of maize and cotton and nonorganic, non-*Bt* varieties with typical insecticide use, the report concluded that *Bt* crops can promote biodiversity. However, if the comparison is with absence of insecticide application, biodiversity was similar or lower with *Bt* crops. The report's conclusions were based on meta-analyses, in which the results of a large number of laboratory and field studies were synthesized, and the weight of evidence depended on sample sizes, differences in means, and variability in the data (Marvier et al., 2007; Wolfenbarger et al., 2008). Later field studies broadened the crops and species under consideration and arrived at similar conclusions (Lu et al., 2014; Neher et al., 2014). Hannula et al. (2014) reviewed the literature on potential effects of *Bt* crops on soil fungi. They found a high degree of variation among studies and concluded that more careful research approaches should be used to examine the crops case by case. As more is learned about the root microbiome, the feasibility of such studies will increase. There remains a need for continued meta-analyses and development of databases to aid in assessment of the effects of *Bt* crops on overall biodiversity. One such effort was under way for maize when the committee wrote its report (Romeis et al., 2014).

There is special concern about the effects of *Bt* maize pollen and nectar on honey bees because of their critical role in pollinating other crops. Duan et al. (2008) conducted a meta-analysis of 25 studies of *Bt* toxin effects on honey bee larvae and adults. They concluded that there was no evidence of any adverse effect on the honey bee but that "additional studies in the field may be warranted if stressors such as heat, pesticides, pathogens, and so on are suspected to alter the susceptibility of honey bees to Cry protein toxicity." There is almost no *Bt* protein in nectar and little in pollen, so exposure of the honey bees is low. When honey bees were exposed to a dose that was about 50 times the dose expected from foraging on *Bt* maize varieties, there was no mortality, but there was some effect on learning by adults (Ramirez-Romero et al., 2008). The committee did not find any studies of the interaction of *Bt* pollen and exposure to neonicotinoid insecticides. In a review of honey bee toxicology, Johnson (2015) concluded that evidence from many studies indicates that *Bt* pollen and nectar are not harmful to honey bees. A 2013 National Research Council report raised concerns about the potential for synergistic interactions between toxins (NRC, 2013). The committee did not find studies that tested for synergy between *Bt* toxin in pollen and honey bee exposure to other toxins and stresses.

Herbicide-Resistant Crops and Weed Biodiversity

For HR crops, there is concern that the efficiency of post-emergence treatment with glyphosate is so high that it decreases weed abundance and diversity. That reduction in turn could affect vertebrate and invertebrate diversity (Lundgren et al., 2009). There have been shifts in the predominant weeds found in maize and soybean due to use of glyphosate-resistant varieties, as discussed above, but Owen (2008) and Johnson et al. (2009) found that the effects on weed biodiversity have been much less than initially expected and more complex. When weeds were controlled by a single application of glyphosate to HR maize and soybean, there was typically greater weed diversity and abundance than when other herbicides were applied to the non-GE counterparts. However, in HR sugar beet treated with glyphosate, weed abundance was much lower than in non-GE sugar beet. In canola weed density was greater in the glyphosate-treated HR crop system than in the non-GE crop system early in the season but lower at another time of the season, while in maize weed density was always higher in the GE crop system (Heard et al., 2003).

Young et al. (2013) and Schwartz et al. (2015) reported results of a detailed U.S. study of weed seedbanks and aboveground weeds on 156 farm field sites in six states in the Southeast and the Midwest. The studies examined several cropping systems: a single continuous HR crop, a rotation of two HR crops, and a rotation of an HR crop with a non-HR crop. They found that the diversity of the weed community in farmers' fields of maize, cotton, and soybean was strongly affected by geographical location and by the previous year's crop. The cropping system had effects on specific weeds, but the overall diversity of weeds was affected much more strongly by location than by the cropping system. Schwartz et al. (2015:437) concluded that "diversification of the weed community, both in the weed seedbank and aboveground, is reflective of geographic region, cropping system being implemented and crop rotation, but not frequency of the use [of] the [glyphosate-resistant] crop trait." Schwartz et al. emphasized that how the HR trait is integrated with other weed control strategies will determine the local weed composition.

Effects of Genetically Engineered Traits on Crop Diversity on Farms

Maintaining a diversity of crop species on farms and a diversity of varieties of each crop on a farm is generally considered to provide a buffer against outbreaks of insect pests and pathogens and insurance against year-to-year environmental fluctuations that could be especially damaging to one crop or variety (Hajjar et al., 2008; Davis et al., 2012; Mijatović et al., 2013). The committee received comments indicating concern that the adoption of GE crops was resulting in reduction of diversity in crops and varieties. It also heard from presenters that GE crops were crucial enablers for implementing specialized crop rotations.

Effect of Genetically Engineered Traits on Diversity of Crop Species. In a survey of U.S. counties from 1978 to 2012, Aguilar et al. (2015) found that the diversity of crop species had decreased by about 20 percent from 1987 to 2012. The decline was especially noticeable in the Midwest. It is difficult to attribute any of the change to the advent of GE crops inasmuch as no change in the trend since 1996 would generally fit the pattern of increased use of GE crops. Furthermore, commodity prices, costs of such inputs as seed and fertilizer, subsidies and societal priorities, water availability, and climatic conditions influence farmers' choices about what to plant (NRC, 2010b). U.S. federal and state policies and their associated incentives have a powerful influence, as evidenced by the majority of U.S. farmland's being managed in compliance with federally mandated Farm Bill guidelines in order to attract commodity payments or other subsidies (NRC, 2010b). Some subsidy programs and policies—such as the Energy Independence and Security Act of 2007 (110 P.L. 140), which establishes targets for use of renewable fuels, including biofuels made from maize and soybean—encourage planting of increased areas of commodity crops with concomitant decreases in crop diversity (Heinemann et al., 2014).

At the individual farm level in the United States, there is little evidence of a substantial shift toward continuous cropping (3 or more consecutive years of a single crop) of maize, soybean, and wheat since the introduction of GE maize and soybean (Wallander, 2013; Figure 4-9). In the Midwest, however, there is a pattern somewhat different from that in the rest of the United States: a doubling in frequency (from about 3.5 percent to about 7 percent) of continuous planting of maize for 4 consecutive years (Plourde et al., 2013). That pattern probably reflects maize prices.

Successful management of very large areas of these crops without rotation may be facilitated by GE varieties with HR or IR traits because these traits give farmers the flexibility to reduce tillage, reduce pesticide use, reduce reliance on crop rotation for weed or insect control, and re-

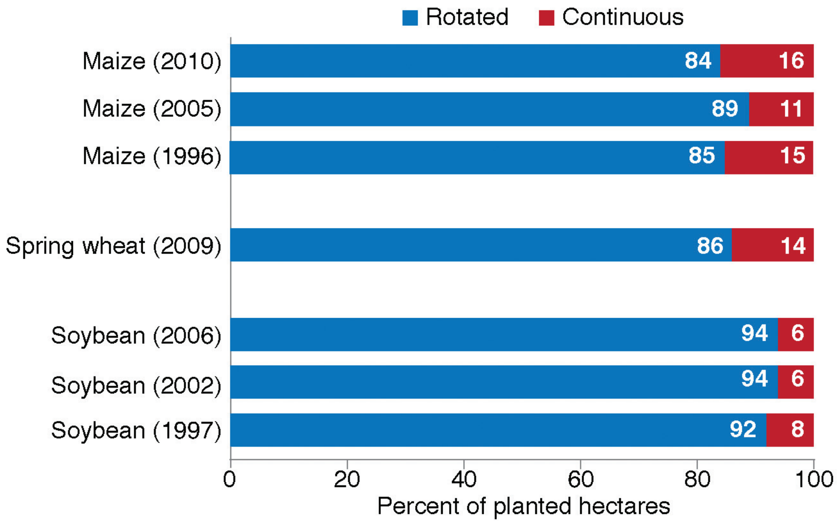

FIGURE 4-9 Percentage of planted hectares under continuous and rotational plantings of maize, spring wheat, and soybean in the United States, 1996–2010.
SOURCE: From Wallander (2013).

duce the use of herbicides with long residual times that can harm certain rotational crops. The committee heard from a USDA research entomologist (Lundgren, 2015) that the adoption of *Bt* maize made it easier for farmers to shift to maize monocropping (for example, when maize prices were high). Several recent studies that used U.S. Census of Agriculture Data, Cropland Data Layer (CDL), and digitized aerial photographs (especially those of smaller land areas than that of the Corn Belt) show that locations with high adoption rates of GE varieties had increased use of a short crop rotation of only maize and soybean. Fausti et al. (2012) showed that adoption of GE maize and soybean in South Dakota was faster than in any other state, with maize area planted with *Bt* or stacked GE hybrids increasing from 37 percent in 2000 to 71 percent in 2009. Over the same period, the proportion of cropland area planted to maize and soybean roughly doubled, from less than 25 percent to about 50 percent of planted hectares. Another possible cause of the shift is increased irrigation development, but increasing prices of both maize and soybean (especially in 2007–2009) are likely drivers and underscore the difficulties in attributing changes in cropping patterns to genetic-engineering technology.

The committee heard a presentation from an invited farmer (Hill, 2015), who indicated that some farmers rely on GE varieties of row crops to control weeds and enable crop rotations that include non-GE vegetables and other non-GE crops in which weed control is otherwise prohibitively expensive or difficult. For those farmers, GE crops are enabling the maintenance of more diverse cropping systems.

Effect of Genetically Engineered Traits on Genetic Diversity Within Crop Species. There is no doubt that genetic diversity within major crop species planted globally has declined over the last century. Gepts (2006:2281) points out that "in Mexico, only 20% of the maize types recorded in 1930 can now be found. Only 10% of the 10000 wheat varieties grown in China in 1949 remain in use."

Although the number of varieties has declined, a meta-analysis of 44 journal articles examining trends from the 1920s through the 1990s in molecular-level (DNA marker) diversity among modern crop varieties of eight crops—including maize, soybean, and wheat—found no general loss of diversity over all crops but some increases and decreases in specific crops (van de Wouw et al., 2010). An invited presenter cautioned that widespread planting of varieties containing the same one or few successful GE trait insertion events that are backcrossed into many breeding lines could decrease genetic diversity and render a crop vulnerable to any pathogen or stress that may evolve to thrive on varieties containing flanking sequences of the single insertion event (Goodman, 2014). For example, a single insertion event of the *Bt* toxin Cry1Ac in cotton is found throughout the world, often based on five or fewer backcrosses (Dowd-Uribe and Schnurr, 2016). The committee could find no evidence of a GE crop that resulted in lower genetic diversity and unexpected pathogen or stress problems, but there is evidence that, in breeding sorghum (*Sorghum bicolor*) for non-GE resistance to greenbug (*Schizaphis graminum*), there was a decline in overall genetic diversity of planted sorghum (Smith et al., 2010). That development points to the need for global monitoring of genetic diversity in crops. As made clear from the studies reviewed by van de Wouw et al. (2010) and later studies of genetic variation in crop varieties (for example, Smith et al., 2010; Choudhary et al., 2013), tools for careful monitoring of loss in genetic diversity are available if researchers can gain access to patented GE varieties of crops to conduct genetic analyses.

> **FINDING: Planting of *Bt* varieties of crops tends to result in higher insect biodiversity than planting of similar varieties without the *Bt* trait that are treated with synthetic insecticides.**
>
> **FINDING: In the United States, farmers' fields with glyphosate-resistant GE crops sprayed with glyphosate have similar or more weed biodiversity than fields with non-GE crop varieties.**
>
> **FINDING: 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. Studies could not be found that tested for a cause–effect relationship between GE crops and this pattern. Changes in commodity prices might also be responsible for this pattern.**
>
> **FINDING: Although the number of available crop varieties declined in the 20th century, there is evidence that genetic diversity among major crop varieties has not declined in the late 20th and early 21st centuries since the introduction and widespread adoption of GE crops in some countries.**

Effects of Genetically Engineered Crops at the Landscape and Ecosystem Levels

The discussion in the section above was confined to potential effects of GE crops on biodiversity on farms themselves. However, the committee also sought evidence of effects of GE crops on loss of the biodiversity found in natural environments, on population loss in species that move between farms and natural environments, and on the potential effects of genes from GE crops on adjoining unmanaged plant communities and on farms without GE crops. Finally, the committee assessed evidence that GE crops have resulted in greater adoption of no-till and reduced-till cropping systems that can have beneficial effects on farms and beyond.

Genetically Engineered Crops and the Expansion of Agriculture into Unmanaged Environments

On the basis of the data presented on the effects of GE crops on biodiversity on farms, there is evidence of some changes in the specific weeds in fields due to herbicides used in association with GE crop varieties, although the overall plant biodiversity does not seem to change substantially (Young et al., 2013; Schwartz et al., 2015). However, the expansion of row crops into previously unmanaged environments is well known to cause a loss of plant and animal biodiversity (Tilman et al., 2001). If GE crops enable expansion of row crops into unmanaged areas, they are likely to affect landscape biodiversity.

Wright and Wimberly (2013) documented a net loss of grasslands of 530,000 hectares in the United States from 2006 to 2010. The land was converted to row crops from a number of environmentally sensitive land forms, including wetlands, highly erodible land, and land in the Conservation Reserve Program (a federal government program that pays farmers to take environmentally sensitive land out of production). Lark et al. (2015) reported similar changes from 2008 to 2012; their sampling indicated that about 0.42 million hectares (or about 14 percent) of the total recent conversion came from land sources that had not been cultivated for more than four decades. Although there is no analysis of whether adoption of GE crops played some part in fueling the conversion of natural lands to maize and other crops, the conversion appears mostly to be a response to both increased demand for liquid biofuels and rapidly increasing crop prices rather than to adoption of genetic-engineering technology, which was already widespread before the largest conversions of unmanaged lands.

Since the commercialization of glyphosate-resistant crops, there has been an expansion of soybean area in Argentina (Grau et al., 2005; Gasparri et al., 2013) and Brazil (Morton et al., 2006; Vera-Diaz et al., 2009; Lapola et al., 2010). The committee searched for information on whether any of the expansion was augmented or hastened by the use of GE soybean. Kaimowitz and Smith (2001) and Grau et al. (2005) argued that improvement in soybean varieties, including the glyphosate-resistance trait, enhanced expansion of soybean area, but they presented no evidence that the glyphosate-resistant trait itself was involved. It is generally possible for HR traits to enhance expansion of crops on previously diverse unmanaged lands, but the committee could not find any compelling evidence that such expansion has occurred.

Genetically Engineered Crops, Milkweed, and Monarch Butterflies

Some concerns over the effect of GE crops on landscape biodiversity focus on communities of thousands of species, but one species has drawn more attention than any other in North America. Worries about effects of *Bt* maize on monarch butterflies began with the publication of laboratory experiments that demonstrated substantial effects of *Bt* maize pollen on growth and survival of monarch larvae (Losey et al., 1999). Because the monarch travels long distances and feeds in agricultural and non-agricultural areas, concern about the potential for death due to *Bt* was reasonable. Controversy over the validity of the research by Losey et al. (1999) and other research that did and did not find adverse effects on the monarch butterfly finally resulted in detailed, coordinated studies funded by U.S. and Canadian government agencies, universities, and industry. Results of these studies were peer-reviewed and published as six articles in the *Proceedings of the National Academy of Sciences of the United States of America* (Hellmich et al., 2001; Oberhauser et al., 2001; Pleasants et al., 2001; Sears et al., 2001; Stanley-Horn et al., 2001; Zangerl et al., 2001). The 2002 National Research Council report *Environmental Effects of Transgenic Plants* provided a detailed discussion of these studies (NRC, 2002:71–75) and concluded that one transgenic event in maize, *Bt*176, posed a risk to monarchs because of high levels of *Bt* toxin in the pollen, but that the vast majority of the *Bt* maize that was being grown in the United States did not pose such a risk. *Bt*176 was later removed from the market, thereby eliminating risk posed by that variety to monarch butterflies or other pollinators. The 2002 National Research Council report saw this portfolio of coordinated studies conducted with transparency and open access to data and supported by diverse funders as a model for dealing with controversial GE crop issues and suggested that “present public research programs, such as in Biotechnology Risk Assessment and Risk Management, will need to be expanded substantially”; the report specifically pointed to the USDA Biotechnology Risk Assessment Research Grants Program in this regard (NRC, 2002:197–198). The committee agrees with the recommendation of the 2002 committee because it has become clear that when studies are or are perceived to be controlled by the developers of the technology the legitimacy of the work is often questioned.

In addition to the potential for a direct effect of *Bt* maize on monarch butterfly populations, it is possible that HR crops indirectly affected monarch populations if they resulted in reducing the abundance of milkweed plants, which are the sole food source for monarch caterpillars. Hartzler (2010) documented a 90-percent decline in the area within Iowa agricultural fields occupied by milkweed from 1999 through 2009 that was due primarily to the use of glyphosate. Pleasants and Oberhauser (2013) used those data and other data on abundance of milkweed in noncrop areas of Iowa to estimate the overall decline in milkweed. They estimated that milkweed abundance declined by 58 percent from 1999 to 2010; but on the basis of data showing more eggs laid on milkweed plants within crops, there was an estimated 81-percent decline in potential production of monarchs in Iowa. Data at that level of detail are not available for other areas of the monarch range. (Of course, decline in milkweed is likely to have been beneficial to some farmers but the specific impacts of milkweed on maize and soybean profitability are not available.)

There are data that demonstrated a decline in the density of monarchs at overwintering sites in Mexico. The average total hectares occupied by dense aggregations of adults during the winters of 1995–2002 was about 9.3, but the average for 2003–2011 was 5.5 with a general trend of decline (Brower et al., 2012). The decline has continued to below 0.7 hectares in 2014, but it was expected to increase in 2015 to 3–4 hectares (Yucatan Times, 2015).

The cause–effect relationship between lower abundance of milkweed in the United States and decreasing overwintering populations is uncertain. If lower abundance of milkweed is limiting the monarch populations, there is expected to be an indication of it in their population dynamics beyond winter habitats in Mexico. A series of articles published in 2015 examined data from researchers and citizen scientists collected in 1995–2014 on dynamics of monarch populations as they moved north in spring and began moving south in fall (Badgett and Davis, 2015; Crewe and McCracken, 2015; Howard and Davis, 2015, Nail et al., 2015; Ries et al., 2015; Steffy, 2015; Stenoien et al., 2015). There was year-to-year variation in the population sizes but little evidence of decline of the monarchs during that period. A general conclusion from the work was that “while the overwintering population (and early spring migration) appears to be shrinking in size, these early monarchs appear to be compensating with a high reproductive output, which allows the subsequent generations of monarchs to fully recolonize their breeding range in eastern North America” (Howard and Davis, 2015:669). The researchers recommended more detailed studies to understand what causes the fall decline. That recommendation was echoed in a paper by Inamine et al. (2016) that also could find no evidence that lower abundance of milkweed resulted in monarch decline. The authors hypothesized that such factors as low nectar abundance and habitat fragmentation could be affecting survival during fall migration.

Pleasants et al. (2016) critiqued the conclusion of no evidence of a decline drawn by Howard and Davis (2015), and Pleasants et al. have been rebutted in turn by Dyer and Forister (2016). Without detailed data, it is difficult to exclude the possibility that declines in the overwintering populations were caused by extreme weather events or parasites and pathogens.

Resolving this debate will require modeling and direct experimental assessment of the extent to which milkweed abundance affects monarch population size. A long-term study providing a complete life-cycle analysis of the monarch butterfly is called for.

The National Research Council reports, *Genetically Modified Pest-Protected Plants: Science and Regulation* (NRC, 2000) and *Environmental Effects of Transgenic Plants* (NRC, 2002) and Marvier et al. (2007) called for spatially explicit national-scale databases on GE crop plants, associated farming practices, and environmental data so that many of the questions surrounding sustainability and genetic-engineering technology could be answered. At the time of its review in 2015, the committee found such databases to be inadequate. That limits the ability to assess effects on abundance of monarchs and many other species.

Dispersal of Genes from Genetically Engineered Crops to Wild Species

Gene flow is the change in gene frequency in a population due to the introduction of a gene or genes through gametes, individuals, or groups of individuals from other populations (Slatkin, 1987). Seed, pollen, and spread by vegetative growth are considered in evaluating gene flow from GE crops to populations of wild relatives. The magnitude of gene flow via pollen depends on many factors, including pollination biology, inheritance of the trait, size of pollen source and sink, and pollen viability over time and distance. Gene flow in the field between compatible plants can occur when they are close enough for pollen to reach a receptive stigma, the plants have synchronous flowering, and there are no reproductive barriers.

Gene flow from GE crops via pollen to other sexually compatible species has long fueled the debate over the introduction of GE crops (for example, Snow and Palma, 1997). Many early concerns were based on the assumption that gene flow would increase the weediness of related species (Wolfenbarger and Phifer, 2000). However, GE crops approved as of 2015, especially in North America, have few sexually compatible weed species or naturalized plant species with which they could hybridize, so the focus has changed to emphasis on gene flow from GE to non-GE crops. The introduction of a GE crop with more sexually compatible wild species could have outcomes different from those observed so far. Release of a GE crop in the crop's center of origin also has raised concerns about the preservation of genetic resources (Kinchy, 2012). If gene flow from a GE crop to a GE crop relative resulted in expression of a *Bt* toxin and that species was now protected from herbivore pests, it could outcompete other closely related species and decrease biodiversity. There is no evidence of such an occurrence.

Movement of a herbicide-resistant transgene to a related species has not been reported to increase competitiveness or weediness in the absence of the herbicide. However, the selection pressure from the use of a herbicide will allow populations to expand as susceptible plants are removed. Populations of HR alfalfa, canola, and creeping bentgrass (*Agrostis stolonifera*) produce feral populations that survive outside cultivation, increase with selection pressure from herbicides, and continue to be a transgene pollen source (Knispel et al., 2008; Zapiola et al., 2008; Schafer et al., 2011; Bagavathiannan et al., 2012; Greene et al., 2015).

GE glyphosate-resistant feral alfalfa was found in seed production areas of California, Idaho, and Washington in 2011 and 2012. Twenty-seven percent of 404 sites where feral alfalfa plants were collected had GE plants (Greene et al., 2015). The authors did not determine if the feral populations were from seed or pollen dispersal. Although there are no wild or native species in the United States with which alfalfa can hybridize, feral populations will increase if glyphosate is the only herbicide used on roadsides and noncrop areas for vegetation management.

There are many reports of GE canola establishing outside cultivation (Pessel et al., 2001; Aono et al., 2006; Knispel and McLachlan, 2010; Schafer et al., 2011). Canola will cross with multiple related species (Warwick et al., 2003). Warwick et al. (2008) identified hybrids between GE herbicide-resistant *Brassica napus* (canola) and a weedy population of *B. rapa*. Multiple generations of crosses were identified in the population, which indicated that the transgene had persisted and was being transmitted over generations. Only one advanced backcross hybrid was found in the population, which showed that transgene introgression is rare in this system. The hybrids were reported to have reduced fitness, including reduced pollen viability, but the transgene persisted over a 6-year period. During that period, herbicide selection pressure did not occur. The results of this study indicate that transgenes may persist but competitiveness would not increase unless the herbicide is applied. Warwick et al. (2008:1393) concluded that “at present, there are no compelling data to suggest that the presence of an HR transgene in a wild or weedy relative is inherently risky.”

When the committee wrote its report, populations of glyphosate-resistant creeping bentgrass were still present in Oregon 13 years after seed-production fields were removed, despite yearly removal of GE plants (Mallory-Smith, personal observation). Populations of the glyphosate-resistant creeping bentgrass were identified in 2010 in Malheur County, Oregon, where no permit was issued for its production (Mallory-Smith, personal observation). Glyphosate-resistant bentgrass was selected because of the use of glyphosate for weed management on irrigation canals. It had spread over hundreds of kilometers of canals by the time it was identified and mitigation efforts were initiated. Creeping bentgrass hybridizes with wild and naturalized compatible relatives. Hybrids between the GE creeping bentgrass and wild and naturalized compatible species were identified outside cultivation (Reichman et al., 2006; Zapiola and Mallory-Smith, 2012). Hybridization, further introgression, and selection pressure from glyphosate use on roadsides and waterways make it likely that the trait will remain in the environment.

There have been no field reports of increased competiveness from gene flow from *Bt* crops to related wild species. In one research study, transfer of the *Bt* trait from GE sunflowers to wild sunflowers reduced insect feeding injury on the wild sunflowers and increased their fecundity (Snow et al., 2003). In another research study, a *Bt* transgene was transferred from *Brassica napus* to wild *B. juncea*, and the progeny were backcrossed to produce a second generation of backcross offspring (Liu et al., 2015). In research plots, the *Bt* plants produced more biomass in pure stands with or without insect pressure than did the susceptible plants. In mixed stands, however, the susceptible plants produced more seeds when insects were not present than when insects were present. As the proportion of *Bt* plants increased with insect feeding pressure, biomass and seed production increased, indicating that the presence of the *Bt* plants may have provided a level of protection for the susceptible plants. In both cases, it is possible that gene flow would provide an advantage to wild populations over time. However, it should be noted that these are research studies with plants that have not been in commercial use.

FINDING: Although gene flow has occurred, no examples have demonstrated an adverse environmental effect of gene flow from a GE crop to a wild, related plant species.

Herbicide-Resistant Crops, Reduced Tillage, and Ecosystem Processes

No-till and reduced-till agricultural practices are known for decreasing wind and water erosion of soil (Montgomery, 2007). There are also claims that no-till and reduced-till agriculture often leads to enhanced soil carbon sequestration and reduces greenhouse-gas emissions (Barfoot and Brookes, 2014). However, many reports that claimed increases in soil carbon suffered methodological flaws: they failed to account for increases in soil bulk density and the lack of soil mixing under no-till (Ellert and Bettany, 1995; Wendt and Hauser, 2013). Other authors concluded that no-till has only a weak effect, if any, on greenhouse-gas emissions even when no-till is combined with mulch retention (Baker et al., 2007; Giller et al., 2009; Powlson et al., 2014). From an environmental perspective, the decrease in soil erosion alone is important.

The adoption of no-till and reduced-till methods began in the 1980s, and the rate of adoption increased because of a combination of factors: the advent of inexpensive and effective herbicides, development of new machines to facilitate direct planting, and, in the United States, a new soil-conservation policy under the Food Security Act of 1985. Those factors favored the use of conservation tillage, in which soil cover of at least 30 percent is maintained as crop residues or other mulch to reduce erosion. Thus, the greatest expansion of no-till and conservation tillage and the concomitant reductions in soil erosion actually predate the release of the first HR varieties of maize and soybean in 1996 (NRC, 2010a).

The National Research Council report on the impacts of GE crops in the United States (NRC, 2010a) reviewed several studies that indicate that farmers who adopted HR crops were more likely to practice conservation tillage and vice versa. During the period 1997–2002, there was an increase in HR crops and conservation tillage (including no-till), but the direction of causation was not clear (Fernandez-Cornejo et al., 2012). In 1997, some 60 percent of the land planted with HR soybean was under no-till or conservation tillage compared with 40 percent of the land planted with non-GE soybean (Fernandez-Cornejo and McBride, 2002).

Adoption of HR varieties may have resulted in farmer decisions to use conservation tillage, or farmers who were using conservation tillage may have adopted HR crops more readily. The work of Mensah (2007) established a "two-way causal relationship": both causal relationships were occurring at the same time. Fernandez-Cornejo et al. (2012) used state-level data from primary soybean-producing states to explore the causal relationships further and changes in herbicide use. Unlike previous researchers, they found that "HR soybean adoption has a positive and highly significant ($P < 0.0001$) impact on the adoption of conservation tillage" in the United States (Fernandez-Cornejo et al., 2012:236–237). They quantified it as an elasticity and found that a 1-percent increase in area of HR soybean resulted in a 0.21-percent increase in conservation tillage. A meta-analysis by Carpenter (2011) stated that from 1996 to 2008, adoption of conservation tillage increased from 51 to 63 percent of planted soybean hectares. Fernandez-Cornejo et al. (2014) also concluded that adopters of HR crops in the United States practice conservation tillage and no-till more than growers of non-GE varieties. That is especially evident with the adoption of HR soybean, although the conclusion also holds for cotton and maize. Those conclusions are based on aggregate trends and do not allow one to determine that the introduction of GE herbicide resistance is causing the adoption of no-till or that the increase in no-till is accompanied by adoption of GE herbicide resistance.

Globally, the effects of HR crop adoption on conservation tillage are less clear because the research has been sparse. The introduction of glyphosate-resistant soybean is cited as a contributing factor in the rapid increase of no-till in Argentina, where adoption of no-till increased from about one-third of soybean area in 1996 to over 80 percent in 2008 (Trigo et al., 2009). Other factors also contributed to the expansion of no-till in Argentina, such as favorable macroeconomic policies, continued promotion efforts, and reduction in herbicide cost. Substantial growth in no-till production also occurred in Canada; from 1996 to 2005, the no-till canola area increased from 0.8 million hectares to 2.6 million hectares, about half the total canola area (Qaim and Traxler, 2005).

FINDING: Both GE crops and the percentage of cropping area farmed with no-till and reduced-till practices have increased over the last two decades. However, cause and effect are difficult to determine.

CONCLUSIONS

There have been strong claims made about the purported benefits and adverse effects of GE crops. The committee found little evidence to connect GE crops and their associated technologies with adverse agronomic or environmental problems. For example, the use of *Bt* crops or HR crops did not result in substantially reduced on-farm biodiversity, and sometimes their use resulted in increased biodiversity. In terms of benefits, the evidence was mixed. *Bt* crops have increased yields when insect-pest pressure was high, but there was little evidence that the introduction of GE crops were resulting in a more rapid yearly increases in on-farm crop yields in the United States than had been seen prior to the use of GE crops. Use of *Bt* crops is clearly associated with a decrease in the number of insecticide applications, but with HR crops the evidence is equivocal. Importantly, most studies only report the number of kilograms of pesticide used, but this metric does not necessarily predict environmental or health effects.

The quantitative contribution of GE crop traits themselves to yield in experimental plots was sometimes difficult to determine because the GE and non-GE varieties could differ in other yield-associated traits. In surveys on yield and insecticide and herbicide use in farmer fields, the different adoption rates of GE crops by farmers who had different land quality and financial resources confounded some results. There is a need for improved survey and experimental approaches that disentangle the effects of the GE trait itself from other factors that affect yield.

The evolution of resistance to *Bt* toxin in insect pests was found to be associated with the use of varieties without a high dose of *Bt* toxin or the absence of refuges. Evolved herbicide resistance in weeds was associated with the overuse of a single herbicide. If GE crops are to be used sustainably, regulations and incentives must be provided to farmers so that more integrated and sustainable pest management approaches become economically feasible.

Overall, the committee found no 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 monarch butterfly populations. Detailed studies of monarch dynamics carried out as of 2015 did not demonstrate an adverse effect related to the increased glyphosate use, but there was still no consensus among researchers that the effects of glyphosate on milkweed has not caused decreased monarch populations.

The committee offers a number of recommendations regarding where investment of public resources in conducting careful experiments and analyses might enable society to make more rigorous assessments of the potential benefits and problems associated with GE crops that would be seen as more legitimate by concerned members of the public than experiments funded by the developers of the technology.

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5

Human Health Effects of Genetically Engineered Crops

In this chapter, the committee examines the evidence that substantiates or negates specific hypotheses and claims about the health risks and benefits associated with foods derived from genetically engineered (GE) crops. There are many reviews and official statements about the safety of foods from GE crops (for example, see Box 5-1), but to conduct a fresh examination of the evidence, the committee read through a large number of articles with original data so that the rigor of the evidence could be assessed.

Some of the evidence available to the committee came from documents that were part of the U.S. regulatory process for GE crops conducted by the U.S. Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), and the U.S. Food and Drug Administration (FDA). Other evidence came from studies published by regulatory agencies in other countries or by companies, nongovernmental organizations (NGOs), and academic institutions. The committee also sought evidence from the public and from the speakers at its public meetings and webinars.[1]

The committee thinks that it is important to make clear that there are limits to what can be known about the health effects of any food, whether non-GE or GE. If the question asked is "Is it likely that eating this food today will make me sick tomorrow?" researchers have methods of getting quantitative answers. However, if the question is "Is it likely that eating

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[1] The committee has compiled publicly available information on funding sources and first-author affiliation for the references cited in this chapter; the information is available at http://nas-sites.org/ge-crops/.

BOX 5-1
Sample of Statements About the Safety of Genetically Engineered Crops and Food Derived from Genetically Engineered Crops

"To date, no adverse health effects attributed to genetic engineering have been documented in the human population." National Research Council (2004)

"Indeed, the science is quite clear: crop improvement by the modern molecular techniques of biotechnology is safe." American Association for the Advancement of Science (2012)

"Bioengineered foods have been consumed for close to 20 years, and during that time, no overt consequences on human health have been reported and/or substantiated in the peer-reviewed literature." Council on Science and Public Health (2012)

"[Genetically modified] foods currently available on the international market have passed safety assessments and are not likely to present risks for human health. In addition, no effects on human health have been shown as a result of the consumption of such foods by the general population in the countries where they have been approved." World Health Organization (2014)

"Foods from genetically engineered plants intended to be grown in the United States that have been evaluated by FDA through the consultation process have not gone on the market until the FDA's questions about the safety of such products have been resolved." U.S. Food and Drug Administration (2015)

"The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research, and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than e.g. conventional plant breeding technologies." European Commission (2010a)

this food for many years will make me live one or a few years less than if I never eat it?" the answer will be much less definitive. Researchers can provide probabilistic predictions that are based on the available information about the chemical composition of the food, epidemiological data, genetic variability across populations, and studies conducted with animals, but absolute answers are rarely available. Furthermore, most current toxicity studies are based on testing individual chemicals rather than chemical mixtures or whole foods because testing of the diverse mixtures of chemicals experienced by humans is so challenging (Feron and Groten, 2002; NRC, 2007; Boobis et al., 2008; Hernández et al., 2013).

With regard to the issue of uncertainty, it is useful to note that many of the favorable institutional statements about safety of foods from GE crops in Box 5-1 contain caveats, for example: "no overt consequences," "no effects on human health have been shown," "are not per se more risky," and "are not likely to present risks for human health." Scientific research can answer many questions, but absolute safety of eating specific foods and the safety of other human activities is uncertain.

The review in this chapter begins with an examination of what is known about the safety of foods from non-GE plants and how they are used as counterparts to those from GE crops in food-safety testing. U.S. food-safety regulatory testing for GE products and GE food-safety studies conducted outside the agency structure are then assessed. A variety of hypothesized health risks posed by and benefits of GE crops are examined, and the chapter concludes with a short discussion of the challenges that society will face in assessing the safety of GE foods that are likely to be developed with emerging genetic-engineering technologies.

COMPARING GENETICALLY ENGINEERED CROPS WITH THEIR COUNTERPARTS

An oft-cited risk of GE crops is that the genetic-engineering process could cause "unnatural" changes in a plant's own naturally occurring proteins or metabolic pathways and result in the unexpected production of toxins or allergens in food (Fagan et al., 2014). Because analysis of risks of the product of the introduced transgene itself is required during risk assessment, the argument for unpredicted toxic chemicals in GE foods is based on the assumption that a plant's endogenous metabolism is more likely to be disrupted through introduction of new genetic elements via genetic engineering than via conventional breeding or normal environmental stresses on the plant. The review below begins by discussing natural chemical constituents of plants in the context of food safety to provide a background on what the natural plant toxins are and how they vary in non-GE plants. The review then goes on to explain the premise used by regulatory agencies to compare GE crops with their non-GE counterparts.

Endogenous Toxins in Plants

Most chemicals of primary metabolism (for example, those involved in the formation of carbohydrates, proteins, fats, and nucleic acids) are shared between animals and plants and are therefore unlikely to be toxic. Perceived risks associated with alterations of plant compounds arise mainly from alterations of plant-specific molecules, popularly known as plant natural products and technically named secondary metabolites. Collectively, there are more than 200,000 secondary metabolites in the plant kingdom (Springob and Kutchan, 2009). Crop species vary in the number of secondary metabolites that they produce. For example, potato (*Solanum tuberosum*) is known for its high diversity of secondary metabolites and can have more than 20 sesquiterpenes (a single group of related compounds), some of which are thought to confer resistance to diseases (Kuc, 1982). The concentrations of these secondary metabolites within some tissues in a particular plant species may vary from high—for example, chlorogenic acids alone make up about 12 percent of the dry matter of green coffee beans (Ferruzzi, 2010)—to trace amounts (many minor saponins in legumes) and may be associated with particular stages of plant development (some found only in seeds) or may increase in response to external stimuli, such as pathogen or herbivore attack, drought, or altered mineral nutrition (Small, 1996; Pecetti et al., 2006; Nakabayashi et al., 2014). Many secondary metabolites function as protective agents, for example, by absorbing damaging ultraviolet radiation (Treutter, 2006), acting as antinutrients (Small, 1996), or killing or halting insects and pathogens that damage crops (Dixon, 2001). Plant secondary metabolites that protect against pathogen attack have been classified as either phytoanticipins (if they exist in a preformed state in a plant before exposure to a pathogen) or phytoalexins (if their synthesis and accumulation are triggered by pathogen attack) (VanEtten et al., 1994; Ahuja et al., 2012). The toxic properties of some plant compounds are understood, but most of these compounds have not been studied. Some secondary metabolites and other products (such as proteins and peptides) in commonly consumed plant materials can be toxic to humans when consumed in large amounts, and examples are listed below:

- Steroidal glycoalkaloids in green potato skin, which can cause gastrointestinal discomfort or, more severely, vomiting and diarrhea.
- Oxalic acid in rhubarb, which can cause symptoms ranging from breathing difficulty to coma.
- Gossypol in cottonseed oil and cake, which can cause respiratory distress, anorexia, impairment of reproductive systems, and interference with immune function in monogastric animals.
- Nonprotein amino acid canavanine in alfalfa sprouts, which can be neurotoxic.
- Hemolytic triterpene saponins in many legume species, which can increase the permeability of red blood cell membranes.
- Cyanogenic glycosides in almonds and cassava, which can cause cyanide poisoning.
- Phototoxic psoralens in celery, which are activated by ultraviolet sunlight and can cause dermatitis and sunburn and increase the risk of skin cancer.

Friedman (2006) provided information that demonstrated that some glycoalkaloids in potato can have both harmful and beneficial effects. The Food and Agriculture Organization has recognized that foods often contain naturally occurring food toxins or antinutrients but that at naturally occurring concentrations in common diets they can be safely consumed by humans (Novak and Haslberger, 2000; OECD, 2000). The health risks associated with some secondary metabolites in common foodstuffs are generally well understood, and the plants are either harvested at times when the concentrations of the compounds are low, the tissues with the highest concentrations of toxins are discarded, or, as in the case of cassava (*Manihot esculenta*), the food is prepared with special methods to remove the toxic compounds. In other cases, food preparation may be the cause of the presence of a toxic compound (for example, the formation of the probable carcinogen acrylamide when potatoes are fried at high temperatures or when bread is toasted). Plant breeders have generally screened for toxins that are typical of the plant group from which a crop was domesticated and have excluded plants that have high concentrations of the compounds.

Unintended changes in the concentrations of secondary metabolites can result from conventional breeding (Sinden and Webb, 1972; Hellenas et al., 1995). In some cases, conventionally bred varieties have been taken off the market because of unusually high concentrations of a toxic compound, as in the case of a Swedish potato variety that was banned from sale in the 1980s because of high concentrations of glycoalkaloids (Hellenas et al., 1995).

Rather than being a cause of worry, many secondary metabolites are perceived as having potential health benefits for humans and are consumed in increasingly large quantities (Murthy et al., 2015). Examples include the isoflavone phytoestrogens found in a number of leguminous plants, such as soybean (*Glycine max*) and clover (*Trifolium* spp.), which have been ascribed beneficial activities, including chemoprevention of breast and prostate cancers, cardiovascular disease, and post-menopausal ailments (Dixon, 2004; Patisaul and Jefferson, 2010). Also, various perceived antioxidants, such as anthocyanins (Martin et al., 2013), and some saponins may have anticancer activity (Joshi et al., 2002). There is, however, disagreement as to whether many of the compounds are beneficial or toxic at the concentrations consumed in herbal medicines or dietary supplements (see, for example, Patisaul and Jefferson, 2010).

FINDING: Crop plants naturally produce an array of chemicals that protect against herbivores and pathogens. Some of these chemicals can be toxic to humans when consumed in large amounts.

Substantial Equivalence of Genetically Engineered and Non–Genetically Engineered Crops

A major question addressed in the regulation of GE crops is whether the concentrations of the toxic secondary metabolites are affected by genetic engineering. In addition to the plant toxins, nutrients, introduced genes, and proteins and their metabolic products in specific GE crops are assessed with a comparative approach that is generally encompassed by the concept of substantial equivalence.

The concept of substantial equivalence has a long history in safety testing of GE foods. The term and concept were "borrowed from the [U.S. FDA's] definition of a class of new medical devices that do not differ materially from their predecessors, and thus, do not raise new regulatory concerns" (Miller, 1999:1042). No simple definition of substantial equivalence is found in the regulatory literature on GE foods. In 1993, the Organisation for Economic Co-operation and Development (OECD) explained that the "concept of substantial equivalence embodies the idea that existing organisms used as food, or as a source of food, can be used as the basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new" (OECD, 1993:14).

The Codex Alimentarius Commission's *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* is careful to state that "the concept of substantial equivalence is a key step in the safety assessment process. However, it is not a safety assessment in itself; rather it represents the starting point which is used to structure the safety assessment of a new food relative to its conventional counterpart" (CAC, 2003:2). The Codex guideline also makes clear that a safety assessment of a new food based on the concept of substantial equivalence "does not imply absolute safety of the new product; rather, it focuses on assessing the safety of any identified differences so that the safety of the new product can be considered relative to its conventional counterpart" (CAC, 2003:2). The OECD (2006) came to a similar conclusion. Conflict among stakeholders often comes into play during the determination of what constitutes evidence of differences from substantial equivalence sufficient to justify a detailed food-safety assessment.

The Codex Alimentarius Commission concluded that the concept of substantial equivalence "aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy to date for safety assessment of foods derived from recombinant-DNA plants" (CAC, 2003:2). Despite some criticism of the substantial-equivalence concept itself (for example, Millstone et al., 1999) and operational problems (for example, Novak and Haslberger, 2000), it remains the cornerstone for

GE food-safety assessment by regulatory agencies. The present committee examined its use in practice and its empirical limitations.

The precautionary principle, which is described in more detail in Chapter 9 (see Box 9-2) is a deliberative principle related to the regulation of health, safety, and the environment and typically involves taking measures to avoid uncertain risks. The precautionary principle has been interpreted in a number of ways, but it is not necessarily incompatible with use of the concept of substantial equivalence. In the case of foods, including GE foods, it can be reasonably argued that even a small adverse chronic effect should be guarded against, given that billions of people could be consuming the foods. However, the degree of precaution taken in the face of uncertainty is a policy decision that varies among countries and according to the specific uncertainty being considered. For example, many European countries and the European Union (EU) as a whole generally take a more precautionary approach with GE foods and climate change whereas the United States has historically taken a more precautionary approach with tobacco products and ozone depletion (Wiener et al., 2011). The reader is directed to Chapter 9 for further discussion of how different regulatory frameworks address uncertainty in the safety of GE foods.

Some differences between a GE food and its non-GE counterpart are intentional and identifiable (for example, the presence of a *Bt* toxin in maize kernels) or are due to practices directly associated with the use of the GE crops (for example, increased use of glyphosate). Some of the risks posed by the intended changes can be anticipated on the basis of the physiological and biochemical characteristics of the engineered change. There are often established protocols for assessing such risks, especially when a change involves exposure to a known toxin. However, other risks have been hypothesized for GE crops because previous uses of a trait (for example, *Bt* as an insecticidal spray) did not have consumption of the GE plant products as the route of exposure. New routes of exposure could result in unanticipated effects.

In contrast with such intended differences, some potential differences between GE crops and their non-GE counterparts are unintentional and can be difficult to anticipate and discern (NRC, 2004). Two general sources of unintended differences could affect food safety:

- Unintended effects of the targeted genetic changes on other characteristics of the food (for example, the intended presence of or increase in one compound in plant cells could result in changes in plant metabolism that affect the abundance of other compounds).
- Unintended effects associated with the genetic-engineering process (for example, DNA changes resulting from plant tissue culture).

Much of the concern voiced by some citizens and scientists about the safety of GE foods is focused on potential risks posed by unintended differences. Some of the biochemical and animal testing done by or for government agencies is aimed at assessing the toxicity of such unintended differences, but what is adequate and appropriate testing for assessing specific toxicities is often difficult to determine. In some cases, the unintended effects are somewhat predictable or can be determined; in such cases, tests can be designed. In other cases, the change or risk could be something that has not even been considered, so the only effective testing is of the whole food itself. As discussed in Chapter 6, there is a tradeoff between costs of such testing and societal benefits of reduction in risks.

The approach of comparing new varieties to existing varieties is just as applicable to crops developed by conventional plant breeding as it is to GE crops (see Chapter 9). The discussion above on endogenous toxins (see section "Endogenous Toxins in Plants") shows that such crops pose some risks. The 2000 National Research Council report *Genetically Modified Pest-Protected Plants* found that "there appears to be no strict dichotomy between the risks to health and the environment that might be posed by conventional and transgenic pest-protected plants" (NRC, 2000:4). Similarly, the 2004 National Research Council report *Safety of Genetically Engineered Foods* found that all forms of conventional breeding and genetic engineering may have unintended effects and that the probability of unintended effects of genetic engineering falls within the range of unintended effects of diverse conventional-breeding methods. The 2002 National Research Council report *Environmental Effects of Transgenic Plants* found that "the transgenic process presents no new categories of risk compared to conventional methods of crop improvement but that specific traits introduced by both approaches can pose unique risks" (NRC, 2002:5). That finding remains valid with respect to food safety and supports the conclusion that novel varieties derived from conventional-breeding methods could be assessed with the substantial-equivalence concept.

FINDING: The concept of substantial equivalence can aid in the identification of potential safety and nutritional issues related to intended and unintended changes in GE crops and conventionally bred crops.

FINDING: Conventional breeding and genetic engineering can cause unintended changes in the presence and concentrations of secondary metabolites.

OVERVIEW OF U.S. REGULATORY TESTING OF RISKS TO HUMAN HEALTH

Although the committee agrees that crops developed through conventional breeding could result in food-safety risks, its statement of task focuses on GE crops. Furthermore, there have been claims and counterclaims about the relative safety of GE crops and their associated technologies compared with conventionally bred crops and their associated technologies. Therefore, the remainder of this chapter examines possible risks and benefits associated with GE crops and assesses the methods used to test them in and beyond government regulatory systems.

Whether testing is done for regulatory purposes or beyond the regulatory realm, it typically involves three categories of testing: acute or chronic animal toxicity tests, chemical compositional analysis, and allergenicity testing or prediction. Although the precision, transparency, specific procedures, and interpretation of results vary among countries, criticisms about the adequacy of testing are not so much country-specific as they are method- and category-specific. For example, there may be arguments about whether a 90-day whole-food animal test is more appropriate than a 28-day test, but the bigger issue is about whether whole-food testing is appropriate. The committee uses a description of the U.S. testing methods as an example, but it mostly examines the criticism of food-safety testing more broadly.

The structure of the U.S. regulatory process for GE crops based on the Coordinated Framework for the Regulation of Biotechnology is briefly reviewed in Chapter 3 and is examined in more detail in Chapter 9. The focus in this chapter is on the testing itself. The present section provides insight into U.S. procedures by describing the risk-testing methods used for two examples of traits in commercialized GE crops: *Bt* toxins and crop resistance to the herbicides glyphosate and 2,4-D.

Regulatory Testing of Crops Containing *Bt* Toxins

EPA considers plant-produced *Bt* toxins to be "plant-incorporated protectants," a class of products generally defined as "a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of that pesticidal substance" (40 CFR §174.3). EPA specifically exempts plant-incorporated protectants whose genetic material codes for a pesticidal substance that is derived from plants that are sexually compatible. *Bt* toxin genes are not exempted because they come from bacteria (see Chapter 9 for regulatory details).

For *Bt* toxins produced by GE crops, EPA took into consideration that there was already toxicity testing of *Bt* toxins in microbial pesticides and that the toxins were proteins that, if toxic, typically show almost immediate toxicity at low doses (EPA, 2001a; also see Box 5-2). The pesticidal safety tests mostly involved acute toxicity testing in mice and digestibility studies in simulated gastric fluids because one characteristic of food allergens is that they are not rapidly digested by such fluids.

Box 5-2 provides a verbatim example of the procedures used for testing as reported in EPA fact sheets for the Cry1F *Bt* toxin so that readers can see what is involved in the testing. The actual research is not typically done by EPA itself. The registrant is usually responsible for testing. Results of the tests of Cry1F show no clinical signs of any toxicity even when Cry1F protein was fed at 576 mg/kg body weight, which would be the equivalent of about ¼ cup of pure Cry1F for a 90.7-kilogram (200-pound) person. Another part of the testing described in Box 5-2 is allergenicity testing. Concerns about the EPA testing methods are discussed in sections below on each category of testing.

Regulatory Testing of Crops Resistant to Glyphosate and 2,4-D and of the New Uses of the Herbicides Themselves

The regulatory actions taken for herbicide-resistant (HR) crops are different from regulatory actions taken to assess *Bt* crops. With *Bt* crops, regulatory actions are related to the crop itself. With HR crops, there are regulatory processes for the plant itself and separate regulatory processes for the new kind of exposure that can accompany spraying of a herbicide on a crop or on a growth stage of a crop that has never been sprayed prior to availability of the GE variety.

EPA governs the registration of herbicides such as glyphosate and 2,4-D. Both glyphosate and 2,4-D were registered well before the commercialization of GE crops. However, EPA has authority to re-examine herbicides if their uses or exposure characteristics change.

A good example of such re-examination was the 2014 EPA registration of the Dow AgroSciences Enlist Duo® herbicide, which contains both glyphosate and 2,4-D for use on GE maize (*Zea mays*) and soybean. Because the glyphosate component of Enlist Duo had already been in use on GE maize and soybean, EPA did not conduct further testing of glyphosate alone. However, 2,4-D was registered previously only for applications to maize up to 20 centimeters tall and for preplant applications to soybean. The proposed use of 2,4-D on GE crops was expected to change use patterns and exposure and thereby triggered a safety assessment of the new use 2,4-D. Additionally, EPA compared the toxicity of the formulation that contained both herbicides to the toxicity of the individual herbicides and concluded the formulation did not show greater toxicity or risk compared to either herbicide alone.

BOX 5-2
Cry1F Testing by the U.S. Environmental Protection Agency

"The acute oral toxicity data submitted support the prediction that the Cry1F protein would be non-toxic to humans. Male and female mice (5 of each) were dosed with 15 % (w/v) of the test substance, which consisted of *Bacillus thuringiensis* var. *aizawai* Cry1F protein at a net concentration of 11.4 %. Two doses were administered approximately an hour apart to achieve the dose totaling 33.7 mL/kg body weight. Outward clinical signs and body weights were observed and recorded throughout the 14 day study. Gross necropsies performed at the end of the study indicated no findings of toxicity. No mortality or clinical signs were noted during the study. An LD50 was estimated at >5050 mg/kg body weight of this microbially produced test material. The actual dose administered contained 576 mg Cry1F protein/kg body weight. At this dose, no LD50 was demonstrated as no toxicity was observed. Cry1F maize seeds contain 1.7 to 3.4 mg of Cry1F/kg of corn kernel tissue.

"When proteins are toxic, they are known to act via acute mechanisms and at very low dose levels [Sjoblad, Roy D., et al. "Toxicological Considerations for Protein Components of Biological Pesticide Products," Regulatory Toxicology and Pharmacology 15, 3-9 (1992)]. Therefore, since no effects were shown to be caused by the plant-pesticides, even at relatively high dose levels, the Cry1F protein is not considered toxic. Further, amino acid sequence comparisons showed no similarity between Cry1F protein to known toxic proteins available in public protein databases.

"Since Cry1F is a protein, allergenic sensitivities were considered. Current scientific knowledge suggests that common food allergens tend to be resistant to degradation by heat, acid, and proteases, may be glycosylated and present at high concentrations in the food.

"Data has been submitted which demonstrates that the Cry1F protein is rapidly degraded by gastric fluid in vitro and is non-glycosylated. In a solution of Cry1F:pepsin at a molar ratio of 1:100, complete degradation of Cry1F to amino acids and small peptides occurred in 5 minutes.

"A heat lability study demonstrated the loss of bioactivity of Cry1F protein to neonate tobacco budworm larvae after 30 minutes at 75 °C. Studies submitted to EPA done in laboratory animals have not indicated any potential for allergic reactions to *B. thuringiensis* or its components, including the δ-endotoxin of the crystal protein. Additionally, a comparison of amino acid sequences of known allergens uncovered no evidence of any homology with Cry1F, even at the level of 8 contiguous amino acids residues."

SOURCE: EPA (2001a).

In the human health risk assessment portion of the EPA Enlist Duo registration document, the following tests and results with 2,4-D were considered (EPA, 2014a):

- An acute dietary test in rats that found a lowest observed-adverse-effect level (LOAEL) of 225 mg/kg (about 1 ounce per 200-pound person).
- A chronic-dietary-endpoint, extended one-generation reproduction toxicity study in rats that found a LOAEL of 46.7 mg/kg-day in females and higher in males.
- Inhalation tests involving data from a 28-day inhalation toxicity study in rats that found a LOAEL of 0.05 mg/L-day.
- Dermal tests that showed no dermal or systemic toxicity after repeated applications to rabbits at the limit dose of 1000 mg/kg-day.
- Reviews of epidemiological and animal studies, which did not support a linkage between human cancer and 2,4-D exposure.

Analysis of the results of those tests and agronomic and environmental assessments resulted in the product's registration.

EPA received over 400,000 comments in response to the initial proposal to register the new use of 2,4-D. Some of the concerns submitted to EPA were similar to ones some members of the public expressed in public comments to the committee, including questions about whether EPA had considered toxicity of only the active ingredient or of the formulated herbicide and whether it had tested for synergistic effects of 2,4-D and glyphosate. EPA (2014b:7) responded that

> acute oral, dermal, and inhalation data, skin and eye irritation data, and skin sensitization data are available for the 2,4-D choline salt and glyphosate formulation for comparison with the 2,4-D parent compound and glyphosate parent compound data, and these test results show similar profiles. The mixture does not show a greater toxicity compared to either parent compound alone. Although no longer duration toxicity studies are available, toxic effects would not be expected as the maximum allowed 2,4-D exposure is at least 100-fold below levels where toxicity to individual chemicals might occur, and exposure to people is far below even that level.

The committee did not have access to the actual data from the registrant.[2]

EPA does not regulate the commercialization of the GE herbicide-resistant crops themselves. That is the role of USDA's Animal and Plant Health Inspection Service (APHIS) under the Plant Protection Act. Under its

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[2] In November 2015, EPA took steps to withdraw the product's registration in light of new information that indicated there could be synergistic effects of the two herbicides, which could possibly result in greater toxicity to nontarget plants (Taylor, 2015). A court ruling in January 2016 allowed the herbicide to remain on the market while EPA considered other administrative actions (Callahan, 2016).

statutory authority, APHIS controls and prevents the spread of plant pests (see Box 3-5). On the basis of a plant-pest risk assessment (USDA–APHIS, 2014a), APHIS concluded that Enlist™ GE herbicide-resistant maize and soybean engineered to be treated with the Enlist Duo herbicide (containing glyphosate and 2,4-D) were unlikely to become plant pests and deregulated them on September 18, 2014 (USDA–APHIS, 2014b). In its document on the decision to deregulate Enlist GE herbicide-resistant maize and soybean (USDA–APHIS, 2014a:ii), APHIS states a general policy that "if APHIS concludes that the GE organism is unlikely to pose a plant pest risk, APHIS must then issue a regulatory determination of nonregulated status, since the agency does not have regulatory authority to regulate organisms that are not plant pests. When a determination of nonregulated status has been issued, the GE organism may be introduced into the environment without APHIS' regulatory oversight."

FDA did not identify any safety or regulatory issues in its consultation with Dow AgroSciences on the Enlist maize and soybean varieties (FDA, 2013). FDA also explained the basis of Dow's conclusion that Enlist soybean is not "materially different in composition" from other soybean varieties (FDA, 2013):

> Dow reports the results of compositional analysis for 62 components in soybean grain, including crude protein, crude fat, ash, moisture, carbohydrates, [acid detergent fiber] ADF, [neutral detergent fiber] NDF, total dietary fiber (TDF), lectin, phytic acid, raffinose, stachyose, trypsin inhibitor, soy isoflavones (i.e., total daidzein, total genistein, total glycitein), minerals, amino acids, fatty acids, and vitamins. No statistically significant differences in the overall treatment effect and the paired contrasts between each of the DAS-44406-6 soybean treatment groups and the control were observed for 29 of the components. A statistically significant difference in the overall treatment effect was observed for 16 components (crude protein, carbohydrates (by difference), NDF, calcium, potassium, cystine, palmitic acid, oleic acid, linoleic acid, linolenic acid, behenic acid, folic acid, γ-tocopherol, total tocopherol, lectin, and trypsin inhibitor). However, differences between the control and the DAS-44406-6 treatment groups were small in magnitude. Differences between DAS-44406-6 soybean and the control were considered not biologically relevant because the mean values were either within the ranges generated using the reference lines, consistent with the ranges of values in the published literature, or both.

FINDING: U.S. regulatory assessment of GE herbicide-resistant crops is conducted by USDA, and by FDA when the crop can be consumed, while the herbicides are assessed by EPA when there are new potential exposures.

FINDING: When mixtures of herbicides are used on a new GE crop, EPA assesses the interaction of the mixture as compared to the individual herbicidal compounds.

Technical Assessment of Human Health Risks Posed by Genetically Engineered Crops

As explained in Chapter 2, the development and use of GE crops is governed by more than national and regional regulatory standards. In the cases of the GE crops commercially available in the United States and some other countries in 2015, inputs from many public and private institutions regarding their specific concerns have influenced the type and extent of GE crop food-safety tests conducted by companies, agencies, and other researchers. Many stakeholders have criticized the testing used by U.S. and other national regulatory agencies for lacking rigor (for example, Hilbeck et al., 2015). Researchers in companies, NGOs, and universities have sometimes conducted more extensive safety tests than are required by national agencies or have reanalyzed existing data, as described below. All testing as of 2015 fell into three categories: animal testing, compositional analysis, and allergenicity testing and prediction.

Animal Testing

Short-Term and Long-Term Rodent Testing with Compounds and Whole Foods. One common criticism of the animal testing conducted by or for regulatory agencies in the United States and elsewhere is related to its short duration (for example, Séralini et al., 2014; Smith, 2014). Indeed, there is a range in the duration and doses within the test protocols used by regulatory agencies that depends in part on the product. Doses for subchronic and chronic toxicity studies are such that the lowest dose (exposure level), which is many times higher than expected for human exposure, is set to ensure that it does not elicit acute adverse effects that would interfere with examining the potential chronic-effect endpoints. As can be seen in the discussion above, EPA conducted an extended one-generation reproduction toxicity study in male and female rats in its assessment of 2,4-D, and it relied on previous long-term studies for the assessment of cancer risk associated with it. For assessment of the *Bt* toxin Cry1F and for the bacterially derived proteins in 2,4-D-resistant maize and soybean, company testing submitted to EPA, FDA, and USDA relied on acute toxicity testing. In all the cases above, the experiments were conducted by adding large amounts of a single test chemical to an animal's diet. Tests with high concentrations of a chemical are typical of EPA testing protocols for pesticides.

What is different between GE crop evaluation and that of general agricultural chemicals is the use of "whole food" tests. These tests are aimed at assessing potential hazards due to the combined intentional and unintentional changes that might have been caused by the genetic engineering of the crop. In such tests, it is not possible to use concentrations higher than what is in the crop itself because potential unintended effects are not typically known. Thus, it is impossible for a researcher to know what compounds should be increased in concentration in a fabricated diet, and the only way to assess such unintended effects is to feed the actual GE crop to test animals. For testing GE maize, soybean, and rice (*Oryza sativa*),[3] flour from kernels or seed is added to an animal's diet and constitutes between about 10–60 percent of the diet. The high percentages can be used because the crop products are nutritious for the animal. In the case of whole foods that are not typically part of a rodent's diet, whether GE or non-GE, it is impossible to achieve very high concentrations of the test food because it would cause nutritional imbalance. The whole-food tests done for regulatory agencies are generally conducted for 28 or 90 days with rats, but some researchers have run tests for multiple generations.

The utility of the whole-food tests has been questioned by a number of government agencies and by industry and academic researchers (for example, Ricroch et al., 2014), and they are not an automatic part of the regulatory requirements of most countries that have specific GE food-testing requirements (CAC, 2008; Bartholomaeus et al., 2013). However, in its 2010 report *A Decade of EU-Funded GMO Research (2001–2010)*, the European Directorate-General for Research and Innovation concluded that "the data from a well-designed 90-day rodent feeding study, together with data covering the gene insert, the compositional analysis, and the toxicity of the novel gene product, form the optimal basis for a comparative assessment of the safety of [genetically engineered] food and its conventional counterpart in the pre-market situation" (EC, 2010a:157). The European Food Safety Authority (EFSA) developed principles and guidance for establishing protocols for 90-day whole-food studies in rodents at the European Commission's request (EFSA, 2011b), and 90-day, whole-food studies were made mandatory by the European Commission (EC, 2013). Most studies reported in the peer-reviewed literature have concluded that there was a lack of adverse effects of biological or toxicological significance (see, for example, Knudsen and Poulsen, 2007; MacKenzie et al., 2007; He et al., 2008, 2009; Onose et al., 2008; Liu et al., 2012), even though some of the studies found statistically significant differences between the GE and non-GE comparator in toxicity.

The criticisms of whole-food tests come from two perspectives. One perspective is that whole-food studies cannot provide useful tests of food

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[3] GE rice was not commercialized in 2015, but GE varieties in development have been tested.

safety because they are not sensitive enough to detect differences (see, for example, Bartholomaeus et al., 2013; Kuiper et al., 2013; Ricroch et al., 2013a, 2014) and that animal testing is not needed because other types of required testing ensure safety (Bartholomaeus et al., 2013; Ricroch et al., 2014). Ricroch et al. (2014) pointed to the costs of the 90-day tests, which they reported as being €250,000 (in 2013 money). The second perspective is that whole-food tests could be useful, but there is concern about their design and conduct or about the parties who conduct them (the companies commercializing the GE crops). That perspective is evident in Séralini et al. (2007), Domingo and Bordonaba (2011), Hilbeck et al. (2015), and Krimsky (2015). Boxes 5-3 and 5-4 describe some of the specific procedures and practices involved in doing these tests.

The committee heard from invited speakers (Entine, 2014; Jaffe, 2014) and members of the public who provided comments at meetings and it received a number of written public comments highlighting the work of one research group (Séralini et al., 2012, 2014) that has conducted a number of whole-food studies of GE herbicide-resistant and insect-resistant crops and

BOX 5-3
Common Procedures for Rodent Toxicity Studies for Safety Evaluation

The most commonly used laboratory animal species are rats and mice of various strains. The normal lifespan of laboratory rat strains varies from 2 to 3 years; that of mice is 18 months to 2 years. There is extensive literature from public-sector and private-sector laboratories on the variables that affect the lifespan of laboratory rats. It includes the source of the animals, whether they are in-bred or out-bred, the type (for example, synthetic, grain-based) and abundance (fixed amounts versus ad libitum feeding) of diets, and housing (single or multiple animals per cage, lighting, air changes, and so on). The studies are designed to examine the overall behavior and well-being of the test animals, such physiological changes as growth, food and water consumption, blood chemistries and hematology, urinalysis, and histopathology. Acute toxicity tests (short-term dosing of a small number of mice or rats for up to 2 weeks) are often done to establish a dose range for the longer-term studies. In an acute toxicity study, the animals are given a wide range of doses to establish the signs of toxicity that may be observed in subacute and subchronic (28-day and 90-day) rodent studies (FDA, 2000a, revised 2007). In general, only a gross-pathology examination is done on animals used in acute toxicity tests. If lesions are observed, a histopathological examination of target tissues may be conducted. On termination of subacute (28-day), subchronic (90-day), and chronic (1-year or longer) studies, a necropsy is done on each animal. Gross and microscopic pathological examinations are conducted on 30 or more individual organs, tissues, or both.

BOX 5-4
Laboratory Practices for Consistency among Studies

Toxicity studies conducted for regulatory purposes—such as those on food additives, pharmaceuticals, and pesticides—are carried out under Good Laboratory Practices (GLP) Guidelines (FDA, 1979; EPA, 1989; OECD, 1998b). The GLP guidelines refer to the quality control that goes into the conduct of laboratory animal-toxicity and efficacy studies. Before promulgation of the GLP guidelines, study designs varied, so reproducibility and quality assurance of many studies were difficult to ascertain. In addition, the GLP guidelines set forth regulations for establishing the levels of compounds to be tested in the animal diet or in the dosage forms used in a study. The GLP guidelines ensure that studies are broadly accepted. The model of the GLP guidelines is generally followed and accepted throughout the world.

of direct consumption of glyphosate. Some comments made to the committee pointed to the publications of that research group as evidence that GE crops and foods derived from GE crops were deleterious to human health; other comments questioned the robustness and accuracy of the research. The committee also heard from the lead researcher himself at one of its meetings (Séralini, 2014). Because of the attention garnered by this specific research group, the committee examined the primary research paper from the group and many articles related to it (Box 5-5).

A general question that remains for all whole-food studies using animals is, How many animals, tested for how long, are needed to assess food safety when a whole food is tested? That question is related to the question of how large an effect the tested food would have to have on the animal for it to be detected with the experiment. The statistical procedure called power analysis can answer the first question, but the committee did not find such analyses in articles related to GE crop whole-food studies. The EFSA scientific committee (EFSA, 2011b) provided general guidance on power analysis. Figure 5-2, from the EFSA report, shows the relationship between the number of experimental units (cages with two animals) per treatment group and the power of an experiment in standard-deviation units. Standard deviations quantify how much the measurement of a trait or effect varies among animals that have been given the same diet. The report concluded that, if researchers follow OECD Test No. 408 of 10 males and 10 females per treatment (OECD, 1998a), a test should be able to detect a difference equal to about 1 standard deviation (with 90-percent confidence) unless the food has a different effect on males and females, in which case, the smallest difference that could be detected would be about 1.5 standard deviations from the experimental mean.

BOX 5-5
Controversial Results of an Animal Feeding Study of Genetically Engineered Crops and Glyphosate

In 2012, Gilles-Éric Séralini and his colleagues published a paper titled "Long Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize" in the journal *Food and Chemical Toxicology* (Séralini et al., 2012).[a] The experimental design, results, conclusions, and presentation of the data were criticized in many letters to the editor of the journal (for example, Berry, 2013; Dung and Ham, 2013; Hammond et al., 2013; Sanders, 2013). In January 2014, the editor-in-chief of the journal published a retraction notice on the basis of criticisms similar to those in the articles cited above (Hayes, 2014). There appear to be many versions of what happened, so the committee reviews some details here. In the notice, the editor-in-chief explained that "the results presented (while not incorrect) are inconclusive, and therefore do not reach the threshold of publication for *Food and Chemical Toxicology*"; he also made clear that "the Editor-in-Chief wishes to acknowledge the co-operation of the corresponding author in this matter, and commends him for his commitment to the scientific process. Unequivocally, the Editor-in-Chief found no evidence of fraud or intentional misrepresentation of the data" (Hayes, 2014:244). Part of the cooperation was in providing all the raw data to the editor and the public. After the retraction, letters to the editor criticized or supported the retraction (for example, Folta, 2014; John, 2014), including a criticism of the retraction by a former editorial board member of the journal (Roberfroid, 2014). Later in 2014, a version of the article with substantial revisions to the text related to the motivation for the experiment and with rewording of the results and discussion but with no changes in the data was republished without peer review in *Environmental Sciences Europe* (*ESEU*) (Séralini et al., 2014) with a comment from the editor on the first page of the article stating that

> Progress in science needs controversial debates aiming at the best methods as basis for objective, reliable and valid results approximating what could be the truth. Such methodological competition is the energy needed for scientific progress. In this sense, ESEU aims to enable rational discussions dealing with the article from G.-É. Séralini et al. (Food Chem. Toxicol. 2012, 50:4221–4231) by re-publishing it. By doing so, any kind of appraisal of the paper's content should not be connoted. The only aim is to enable scientific transparency and, based on this, a discussion which does not hide but aims to focus methodological controversies.

The revised Séralini et al. (2014) article stated that "this study represents the first detailed documentation of long-term deleterious effects arising from consumption of a GMO, specifically a [Roundup]-tolerant maize, and of [Roundup], the most widely used herbicide worldwide." The study started with 5-week-old, virgin albino Sprague-Dawley rats and "was conducted in a Good Laboratory Practice (GLP) accredited laboratory according to OECD guidelines." According to the authors, it was "designed as a chronic toxicity study and as a direct follow up to a previous investigation on the same NK603 [genetically engineered] maize conducted by the developer company, Monsanto" because the authors' re-analysis of the Hammond et al. (2004) study (but not the EFSA reanalysis [2007]) suggested some trends in treatment effects. The same rat strain, maize variety, and herbicide were used as in Hammond et al. (2004). There were 10 treatments in the Séralini et al. study: one control group had access to plain water and a standard diet from the closest isogenic non-GE maize; three groups were fed with 11 percent, 22 percent, and 33 percent of GE NK603 maize treated with Roundup in the field; three groups with the same percentages of GE maize but with no Roundup treatment; and three groups with the non-GE maize diet but with the rats' water supplemented with Roundup at 0.50 mg/L, 400 mg/kg, or 2,250 mg/L. There were 20 rats per group—10 males and 10 females, for totals of 20 control rats and 180 treatment rats. The animals were fed for 2 years, but some animals died before the end of the study. Séralini et al. (2014) measured behavior, appearance, palpable tumors, and infections. They also conducted microscopic examinations and biochemical analysis of blood and urine to look for abnormalities. Average tumor incidence reported by Séralini et al. (2014) was comparable to data on untreated control Sprague-Dawley rats reported by Davis et al. (1956), Brix et al. (2005), and Dinse et al. (2010).

The committee's analysis focused on the tumor data because they have received the most attention from the public and the news media (see, for example, Amos, 2012; Butler, 2012; Johnson, 2014). As can be seen in Figure 5-1, Séralini et al. (2014) measured tumors in all rats over time (shown in the time-series graphs). The bar graphs give the total number of tumors found per group (note that this shows total numbers of tumors, not numbers of rats with tumors, so it assumes that each tumor is an independent occurrence). There were many more tumors in females than in males. The bar on the left shows the number of tumors in the control female group; this number is always lower than the number in the treatment groups. As discussed in the article, there was no relationship between the treatment dose and the number of tumors in females, even in the case of direct glyphosate feeding through water dispensers in which the range of concentration was from 0.50 mg/L to 2,250 mg/L. The authors hypothesized that such a result could make sense if there was a low threshold of the substance that caused the tumors, as could possibly be the case if Roundup were an endocrine disruptor (there is mixed evidence for endocrine disruption from Roundup [Gasnier et al., 2009]). It is important to note that all the bars for the female control groups are the same because the same 10 female rats are always being compared with the different treatment groups. If only three of the female control rats had one extra tumor, the graphs would show no differences. Reanalysis of the data (EFSA, 2012) found no statistically significant differences.

The one major conclusion stated in the republished abstract of Séralini et al. (2014) was that their "findings imply that long-term (2 year) feeding trials need to be conducted to thoroughly evaluate the safety of [GE] foods and pesticides in their full commercial formulations." The comment on the original paper by the editor-in-chief of *Food and Chemical Toxicology* that "the results presented (while not incorrect) are inconclusive" can be seen as refuting the conclusion in the republished study. The results in the republished study suggest that long-term

continued

BOX 5-5 Continued

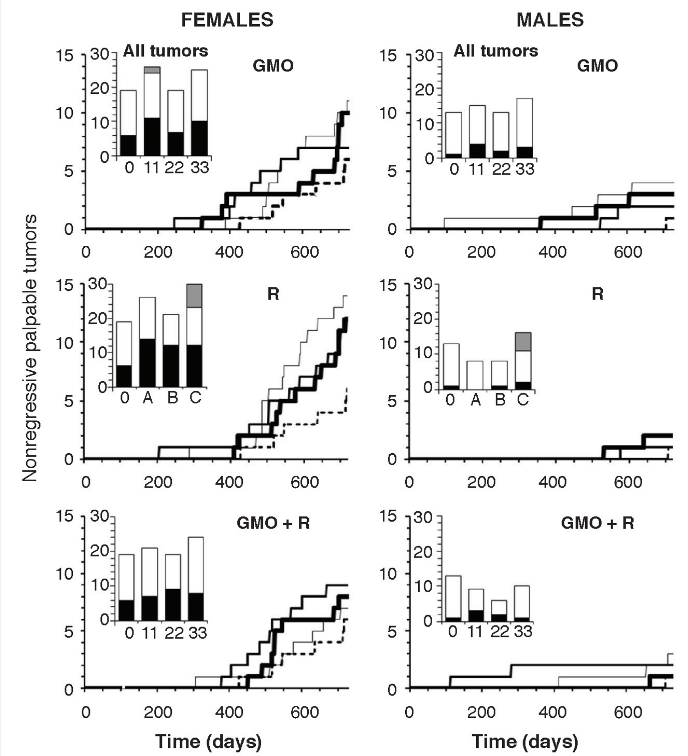

FIGURE 5-1 Nonregressive tumors in rats fed genetically engineered (GE) maize treated or not treated with Roundup and those fed non-GE maize and water treated with Roundup.
SOURCE: Séralini et al. (2014).
NOTE: The “GMO” graphs in the figure are trials in which rats were fed with GE NK603 maize (to which Roundup had or had not been applied) at doses of 11 percent, 22 percent, and 33 percent of their diet (thin, medium, and bold lines, respectively) and compared with closest isogenic non-GE maize control (dotted line). The “R” graphs are trials in which Roundup was administered in the drinking water at three doses (thin, medium, and bold lines, respectively) at environmental levels (A), maximum residue levels in some agricultural GE crops (B), and half the minimal agricultural levels (C). The “GMO + R” graphs are trials in which the treatments included GE maize and Roundup. The largest tumors were palpable during the experiment and numbered from 20mm in diameter for males and 17.5 mm for females. Above this size, 95 percent of growths were nonregressive tumors. Summary of all tumors are shown in the bar histograms in which black represents the nonregressive large tumors, white the small internal tumors, and grey the metastases.

studies with much larger samples be conducted to determine whether there is reason to use 2-year studies generally, but the committee disagrees that this one study should lead to a general change in global procedures regarding the health effects and safety of GE crops.

Many of the published criticisms of the Séralini et al. (2012, 2014) study commented on the small number of animals used in the study and on the strain of rats used. Examination of other whole-food GE crop studies indicates that the numbers of rats and the strain used were typical (Bartholomaeus et al., 2013). Indeed, OECD Test No. 408 for 90-day trials (OECD, 1998a) calls for 10 males and 10 females for each treatment. The criticism of Séralini et al. (2014) is that their analysis included the incidence of tumors, which would require more animals for a robust analysis (EFSA, 2012).

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[a] Roundup is the trademarked name of glyphosate-based herbicides sold by Monsanto.

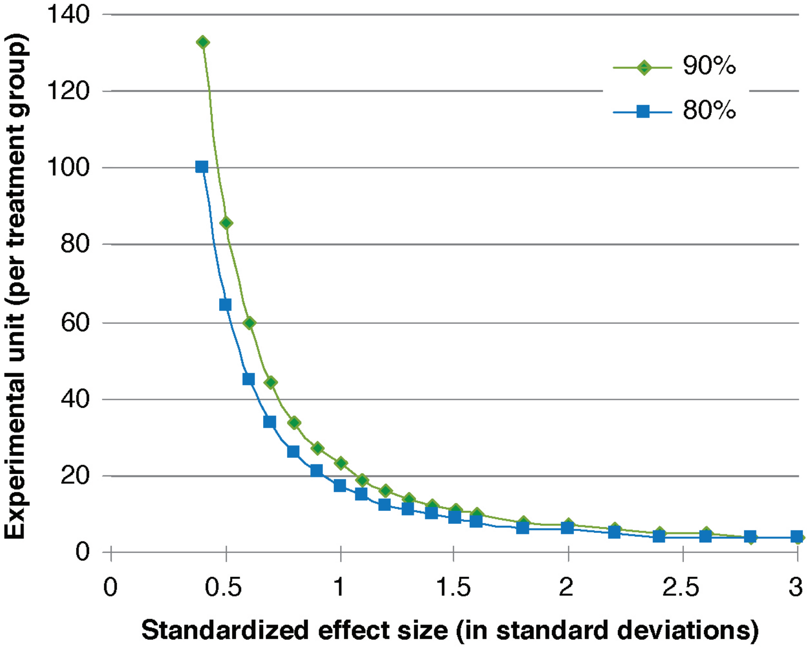

FIGURE 5-2 General statistical information on the number of experimental units needed per treatment group as a function of standardized effect size for 80-percent and 90-percent power and 5-percent significance level using a two-sided t test.
SOURCE: EFSA (2011b).
NOTE: An experimental unit is two animals in a single cage. This figure approximates the situation in a 2 (treatments) × 2 (sexes) factorial design.

Because the relationship is quite abstract for the nonstatistician, the committee examined the size of the standard deviations in a number of whole-food safety articles. It found that the sizes of the standard deviations compared with the mean value of a measured trait depended heavily on the trait being measured and on the specific research article. For example, in the Hammond et al. (2004) study, the average white blood cell count for the four treatments, each with 9 or 10 female Sprague-Dawley rats, is 6.84 10^3/µl, and the average standard deviation is 1.89 10^3/µl. On the basis of rough calculations, this test would have the power to discern statistically whether the GE food caused an increase in white blood cell count of about 35 percent with about 90-percent confidence. If the male white blood cell count effects and standard deviations were similar to those in females, the test could have found about a 25-percent increase.

OECD (1998a) made general recommendations, such as those used in

Hammond et al. (2004), for the number of units (cages with two animals) per treatment. Following these guidelines leads to the assumption that less than a 25-percent change in the white blood cell count was not biologically relevant. The EU Standing Committee on the Food Chain and Animal Health adopted the mandatory use of 90-day whole-food testing of GE crops, and its protocols generally follow OECD guidelines for the testing of chemicals (EC, 2013).

EFSA also published a document (EFSA, 2011c) that focused specifically on the questions, What is statistical significance? and What is biological relevance? The accessibly written document makes clear that the two are very different and that it is important to decide how large a difference is biologically relevant before designing an experiment to test a null hypothesis of no difference. The problem in most whole-food animal studies is in determining how large a biological difference is relevant. Most of the statistically significant differences observed in the literature on the animal-testing data were around a 10- to 30-percent change, but the authors do not give detailed explanations of why they conclude that a statistically significant difference is not biologically relevant. A general statement is sometimes made that the difference is within the range for the species, but because the range of values for the species typically come from multiple laboratories, such a statement is not useful unless the laboratories, instrumentation, and health of the animals were known to be comparable.

Clearly, the European Commission relied on both expert judgment and citizen concerns in making its assessment of biological relevance of the effects of GE foods in requiring 90-day testing. It is reasonable to ask what balance of the two is the basis for this judgment. As pointed out by the 2002 National Research Council report, “risk analysis of transgenic plants must continue to fulfill two distinct roles: (1) technical support for regulatory decision making and (2) establishment and maintenance of regulatory legitimacy” (NRC, 2002:6). Fulfilling the two roles can lead to different country-specific and region-specific decisions. This issue is discussed further in Chapter 9.

One specific criticism of the 90-day whole-food studies revolves around an EU-funded project conducted by Poulsen et al. (2007) in which rice was genetically engineered to produce the kidney bean lectin, agglutinin E-form, which is known to have toxic properties. In a 90-day test, rats were fed diets of 60-percent rice with the lectin gene or 60-percent rice without the lectin gene. The researchers concluded that they did not find any meaningful differences between the two treatments. However, in a treatment in which the diets were spiked with 0.1-percent recombinant lectin (a high dose), biological effects including significant differences in weight of small intestines, stomach, and pancreas and in plasma biochemistry were found. Poulsen et al. included results from a preceding 28-day feeding study and compositional analyses of the rice diets. The criticism involves the question, If a whole-food study with a known toxin does not demonstrate effects, how can the test be considered useful? (Bartholomaeus et al., 2013). If a whole-food study with an animal finds statistically significant effects, there is obviously a need for further safety testing, but when there is a negative result, there is uncertainty as to whether there is an adverse effect on health. In the specific case of lectin gene in rice, one could argue that the statistical power of the whole-food test was insufficient or that, when the toxin is in the structure of the food, it is no longer toxic so the food is safe.

Other Long-Term Studies with Rodents. In addition to the work of Séralini et al. (2012, 2014), there have been other long-term rodent studies, some of which included multiple generations. Magana-Gomez and de la Barca (2009), Domingo and Bordonaba (2011), Snell et al. (2012), and Ricroch et al. (2013b) reviewed the studies. Some found no statistically significant differences, but quite a few found statistically significant differences that the authors generally did not consider biologically relevant, typically without providing data on what was the normal range. In the multigeneration studies, the sire and dam are dosed via the diet before conception, and the parent generation and pups are dosed via the diet throughout the duration of the study to determine multiple generational outcomes, including growth, behavior, and phenotypic characteristics. Some studies have looked at three or four generations. For example, Kiliç and Akay (2008) conducted a three-generation rat study in which 20 percent of the diet was *Bt* maize or a non-*Bt* maize that otherwise was genetically similar. All generations of female and male rats were fed the assigned diets, and the third-generation offspring that were fed the diets were sacrificed after 3.5 months for analysis. The authors found statistical differences in kidney and liver weights and long kidney glomerular diameter between the GE and non-GE treatments but considered them not biologically relevant. Similarly, statistically significant differences were observed in amounts of globulin and total protein between the two groups. There was no presentation of standards used for judging what would be a biologically relevant difference or for what the normal range was in the measurements.

The standard deviations in measurements of the traits (that is, effects) of individual animals in a treatment in the long-term studies were similar to those of studies of shorter duration. Therefore, the power of the tests to detect statistically significant differences was in the range of 10–30 percent. The committee could not find justification for considering this statistical power sufficient. It can be argued that the number of replicates (number of units of two animals per treatment) in the studies should be substantially increased, but one argument against an increase in numbers is related to the ethics of subjecting more animals to testing (EC, 2010b). One could also argue that it is unethical to conduct an underpowered study. However, most if not all of the rodent studies are based on widely accepted safety evaluation protocols with fixed numbers of animals per treatment. Cultural values regarding precaution for human safety and those regarding the number of animals subjected to testing are in conflict in this case. As pointed out by Snell et al. (2012), a close examination of the long-term and multigenerational studies reveals that some have problems with experimental design, the most common being that the GE and non-GE sources were not isogenic and were grown in different locations (or unknown locations). Those problems in design make it difficult to determine whether differences are due to the genetic-engineering process or GE trait or to other sources of variation in the nutritional quality of the crops.

In cases in which testing produces equivocal results or tests are found to lack rigor, follow-up experimentation with trusted research protocols, personnel, and publication outlets is needed to decrease uncertainty and increase the legitimacy of regulatory decisions. There is a precedent of such follow-up studies in the literature on GE crop environmental effects that could serve as a general model for follow-up food-safety testing (see Chapter 4 section "Genetically Engineered Crops, Milkweed, and Monarch Butterflies"). The USDA Biotechnology Risk Assessment Research Grants Program has enabled this approach in a few cases.

Beyond Rodent Studies. Mice and rats are typically used in toxicity studies because of their general physiological similarities to humans and their small size, but some farm animals are considered to be better models of human physiology than rodents. The best example is the pig, which is considered to be better than rodents as a model, especially with respect to nutritional evaluations (Miller and Ullrey, 1987; Patterson et al., 2008; Litten-Brown et al., 2010). Porcine insulin has been used for decades to control blood sugar in patients who have childhood-onset diabetes mellitus (type I diabetes). Pig heart valves are used for human mitral valve replacement, and pig skin has been investigated as a possible donor tissue. The pig is monogastric as is the human, and its gastrointestinal tract absorbs and metabolizes nutrients (lipids and micronutrients) in the same manner as in humans.

Reviews of studies with animals fed GE foods have included studies using both rodents and farm animals (Bartholomaeus et al., 2013; DeFrancesco, 2013; Ricroch et al., 2013a,b, 2014; Swiatkiewicz et al., 2014; Van Eenennaam and Young, 2014). Those animal studies have taken advantage of the fact that maize and soybean are major components of the diets of many farm animals. Some of the reported studies that used farm animals have designs similar to those of rodent studies and have variation in duration and replicates similar to that of the rodent experiments. Some of the tests were run for 28 days (for example, Brouk et al., 2011; Singhal et al., 2011), others for a long term (Steinke et al., 2010) or in multiple generations (Trabalza-Marinucci et al., 2008; Buzoianu et al., 2013b).

The experiments with pigs are especially relevant. Most of them were conducted in one prolific laboratory (Walsh et al., 2011, 2012a,b, 2013; Buzoianu et al., 2012a,b,c,d, 2013a,b). The studies range from examination of short-term growth of piglets to multigenerational studies of sows and piglets, with mixed designs having either generation or both exposed to *Bt* maize and non-*Bt* maize. Characteristics measured included food consumption and growth, assessment of organ size and health, immunological markers, and microbial communities. The authors of the studies generally concluded that *Bt* maize does not affect health of the pigs, but they reported a number of statistically significant differences between *Bt* maize treatment and control maize treatment. In one experiment (Walsh et al., 2012a), the weaned piglets that were fed *Bt* maize had lower feed-conversion efficiency during days 14–30 ($P > 0.007$) but no significant effect over the full span of the experiment. In another experiment (Buzoianu et al., 2013b), there was lower efficiency in the *Bt* treatment during days 71–100 ($P > 0.01$) but again no effect over the full span of the experiment.

In those experiments with pigs and experiments with other farm animals and rodents, there was apparently one source of the GE food and one source of the non-GE food per study, and it is generally not clear that the food sources were isogenic or grown in the same location. That makes it difficult to determine whether any statistical differences found were due to the engineered trait or to the batches of food used, which in at least some experiments varied in nutrient content and may have differed in bioactive compounds (produced in response to plant stressors), which may have a profound effect on outcomes of nutritional studies. Another issue is that many statistical tests were performed in most studies. That could result in accumulation of false-positive results (Panchin and Tuzhikov, 2016). Although this is not a situation in which a stringent correction for doing multiple tests is called for (Dunn, 1961), there is reason to be cautious in interpretation of statistical significance of individual results because multiple tests can lead to artifactual positive results. The issue of multiple test results is common in many fields, and one approach used in genetics is to use the initial tests for hypothesis generation with follow-up experiments that test an a priori hypothesis (for example, Belknap et al., 1996). If a straightforward application of Bonferonni correction is used, each animal study that measures multiple outcomes, whether for GE crops or any other potential toxicant, could require over 1,000 animals to obtain reasonable statistical power (Dunn, 1961).

In addition to the literature on controlled experiments with livestock, Van Eenennaam and Young (2014) reviewed the history of livestock health and feed-conversion ratios as the U.S. livestock industry shifted from non-GE to GE feed. Producers of cattle, milk cows, pigs, chickens, and other livestock are concerned about the efficiency of conversion of animal feed into animal biomass because it affects profit margins. The data examined start as early as 1983 and run through 2011. Therefore, livestock diets shifted from all non-GE feed to mostly GE feed within the duration of the study. Van Eenennaam and Young found that, if anything, the health and feed-conversion efficiencies of livestock had increased since the introduction of GE crops but that the increase was a steady rise, most likely because of more efficient practices not associated with use of GE feed. In the studies that they reviewed, the number of animals examined was large (thousands). Of course, most livestock are slaughtered at a young age, so that data cannot address the issue of longevity directly. However, given the general relationship between general health and longevity, the data are useful.

FINDING: The current animal-testing protocols based on OECD guidelines for the testing of chemicals use small samples and have limited statistical power; therefore, they may not detect existing differences between GE and non-GE crops or may produce statistically significant results that are not biologically meaningful.

FINDING: In addition to experimental data, long-term data on the health and feed-conversion efficiency of livestock that span a period before and after introduction of GE crops show no adverse effects on these measures associated with introduction of GE feed. Such data test for correlations that are relevant to assessment of human health effects, but they do not examine cause and effect.

RECOMMENDATION: 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.

RECOMMENDATION: A power analysis for each characteristic based on standard deviations in treatments in previous tests with the animal species should be done whenever possible to increase the probability of detecting differences that would be considered biologically relevant.

RECOMMENDATION: In cases in which early published studies produced 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.

> **RECOMMENDATION: 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.**

Compositional Analysis

Compositional Analysis of Genetically Engineered Crops. As part of the regulatory process of establishing substantial equivalence, GE crop developers submit data comparing the nutrient and chemical composition of their GE plant with a similar (isoline) variety of the crop. In the United States, submitting such data to FDA is voluntary, although as of 2015 this seems to always be done by developers. Developers and regulators compare key components of the GE variety with published reference guides that list the concentrations and variabilities of nutrients, antinutrients, and toxicants that occur in crops already in the food supply.[4] The section "Regulatory Testing of Crops with Resistance to Glyphosate and 2,4-D and the New Uses of the Herbicides Themselves" earlier in this chapter gives an example of the types of nutrients and chemicals that are generally measured. In the specific case of the soybean resistant to 2,4-D and glyphosate, measurements of 62 components in the soybean were submitted by Dow AgroSciences. There were statistically significant differences between the GE and comparison varieties in 16 of the 62. The differences were considered to be small and within the range of published values for other soybean varieties. They were therefore "considered not biologically relevant." In compositional analysis, as in some of the whole-food animal testing, it is difficult to know how much of the variance and range in values for the components is due to the crop variety, the growing conditions, and the specific laboratory experimental equipment. In the United States, regulatory agencies require that the comparison be between the GE crop and its isogenic conventionally bred counterpart grown in side-by-side plots. In those cases, it is hard to attribute differences to anything but the genetic-engineering process.

> **FINDING: 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.**

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[4] OECD develops consensus documents that provide reference values for existing food crops (OECD, 2015). These are publicly available online at http://www.oecd.org/science/biotrack/consensusdocumentsfortheworkonthesafetyofnovelfoodsandfeedsplants.htm (accessed May 9, 2016). The International Life Science Institute (ILSI) also maintains a crop composition database at www.cropcomposition.org (accessed May 9, 2016). ILSI reports that in 2013 the database contained more than 843,000 data points representing 3,150 compositional components.

Composition of Processed Genetically Engineered Foods. General compositional analysis and the specific content of the introduced proteins are typically conducted on raw products, such as maize kernels or soybean seed. However, much of the human consumption of these products occurs after substantial exposure to heat or other processing. If in processing of foods the amounts of GE proteins substantially increase, consumers are potentially exposed to a risk that is different from that anticipated from testing the raw material. In the production of oil, for example, the goal is to separate the oil from other compounds in the raw crop, such as proteins and carbohydrates. Crude oils can contain plant proteins (Martín-Hernández et al., 2008), but in highly purified oils even sophisticated approaches have failed to find any nondegraded proteins (Hidalgo and Zamora, 2006; Martín-Hernández et al., 2008). Those results are reflected in the fact that people who are allergic to soybean are not affected by purified oils (Bush et al., 1985; Verhoeckx et al., 2015).

A few studies have searched for a means of finding DNA in plant-derived oils to identify the origin of the oil as GE or non-GE for labeling purposes (Costa et al., 2010a,b) or to identify the origin of olive oil (Muzzalupo et al., 2015). It is possible to detect DNA, but the amounts are typically diminished in purified oils to 1 percent or less of the original content. Similarly, Oguchi et al. (2009) were not able to find any DNA in purified beet sugar. Some countries exempt products from labeling if GE protein or DNA is not detectable. For example, in Japan, where foods with GE ingredients typically require labeling, oil, soy sauce, and beet sugar are excluded because of degradation of GE proteins and DNA (Oguchi et al., 2009). Australia and New Zealand have similar exemptions from labeling for such highly refined foods as sugars and oils (FSANZ, 2013).

The detection of GE protein and DNA in other processed foods depends on the type of processing. For example, the amount of the *Bt* protein Cry1Ab detected by immunoassay in tortillas depends on cooking time (de Luis et al., 2009). The detected amount of Cry9C protein remaining in samples of corn bread, muffins, and polenta was about 13, 5, and 3 percent of the amount in the whole-grain maize (Diaz et al., 2002). For Cry1Ab in rice, Wang et al. (2015) found that baking was more effective in lowering the detection using polyclonal antibodies of the Cry1Ab protein than microwaving, but 20 minutes of baking at 180°C left almost 40 percent of the protein intact. Heat denaturation of proteins can lower antibody binding to epitopes and cause lower detection of GE proteins.

FINDING: The amount of GE protein and DNA in food ingredients can depend on the specific type of processing; some foods contain no detectable protein and little DNA. In a few countries that have manda-

tory labeling of GE foods, that is taken into account, and food without detectable GE DNA or GE protein is not labeled.

Newer Methods for Assessing Substantial Equivalence. As explained in Chapter 2, governance of GE crops includes regulatory governance. Although not required to by governing bodies, companies and academic researchers have moved beyond the typical measurements of food composition to newer technologies that involve transcriptomics, proteomics, and metabolomics. The new methods provide a broad, nontargeted assessment of thousands of plant characteristics, including the concentrations of most of the messenger RNAs, proteins, and small molecules in a plant or food. These methods are more likely to detect changes in a GE crop than the current regulatory approaches. If a GE crop has been changed only as intended, any changes observed in these -omics measurements theoretically should be predictable in a given environment. The science behind the methods, including the current limitations of their interpretation, is discussed in Chapter 7. The discussion here focuses on how the methods have already been applied in the assessment of risk of health effects of currently commercialized GE crops.

Ricroch et al. (2011) reviewed -omics data from 44 studies of crops and detailed studies of the model plant *Arabidopsis thaliana*. Of those studies, 17 used transcriptomics, 12 used proteomics, and 26 used metabolomic methods. Ricroch (2013) updated the number of studies to 60. The committee found that many more studies had been done since those reviews were published, and many of them have used multiple -omics approaches. The sophistication of the studies has increased (Ibáñez et al., 2015) and is likely to increase further. As recommended in Chapter 7, there is a need to develop further and share databases that contain detailed -omics data (Fukushima et al., 2014; Simó et al., 2014).

In some studies of GE plants in which simple marker genes were added, there were almost no changes in the transcriptome (El Ouakfaoui and Miki, 2005), but use of other -omics methods has revealed changes (Ren et al., 2009). For example, in a comparison of glyphosate-resistant soybean and non-GE soybean, García-Villalba et al. (2008) found that three free amino acids, an amino acid precursor, and flavonoid-derived secondary metabolites (liquiritigenin, naringenin, and taxifolin) had greater amounts in the GE soybean and 4-hydroxy-l-threonine was present in the non-GE soybean, but not in the GE variety. They hypothesized that the change in the flavonoids may have been because the modified EPSPS enzyme (a key enzyme of the shikimate pathway leading to aromatic amino acids) introduced to achieve glyphosate resistance could have different enzymatic properties that influenced the amounts of aromatic amino acids. The committee was not aware of such a hypothesis before this metabolomic study. (A concern was expressed in a comment submitted to the committee that the EPSPS transgene would cause endocrine disruption. The committee found no evidence to suggest that the changes found by García-Villalba et al. would have such an effect.)

On the basis of previous experimentation, it is predicted that, when a gene for a nonenzymatic protein (such as a *Bt* toxin gene) is added to a plant, there will be very few changes in the plant's metabolism (Herman and Price, 2013). However, when a gene has been added specifically to alter one metabolic pathway of a plant, a number of predicted and unpredicted changes have been found. For example, Shepherd et al. (2015) found that, when they downregulated enzymes (that is, decreased expression or activity) involved in the production of either of two toxic glycoalkaloids (alpha-chaconine and alpha-solanine) in a GE potato with RNA-interfering transgenes that regulated synthesis of one toxic glycoalkaloid, the other compound usually increased. When they downregulated production of both compounds, beta-sitosterol and fucosterol increased. Neither of these compounds has the degree of toxicity associated with alpha-chaconine and alpha-solanine. Other compounds also differed from controls in concentration, but some of the changes may have been due to products generated during the tissue-culture process used in these experiments and not to the transgenes.

Many of the studies have found differences between the GE plants and the isogenic conventionally bred counterparts, but for many components there is more variation among the diverse conventionally bred varieties than between the GE and non-GE lines (Ricroch et al., 2011, Ricroch, 2013). Furthermore, the environmental conditions and the stage of the fruit or seed affect the finding. Chapter 7 addresses the future utility of the -omics approaches in assessing the biological effects of genetic engineering.

FINDING: 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 conventionally bred crop varieties due to genetics and environment.

FINDING: If an unexpected change in composition beyond the natural range of variation in conventionally bred crop varieties were present in a GE crop, -omics approaches would be more likely to find the difference than current methods.

FINDING: Differences in composition found by using -omics methods do not, on their own, indicate a safety problem.

Food Allergenicity Testing and Prediction

Allergenicity is a widespread adverse effect of foods, several plants, tree and grass pollens, industrial chemicals, cosmetics, and drugs. Self-reporting of lifetime allergic responses to each of the most common food allergens (milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish) ranges from 1 to 6 percent of the population (Nwaru et al., 2014). Allergies are induced in a two-step process: *sensitization* from an initial exposure to a foreign protein or peptide followed by *elicitation* of the allergic response on a second exposure to the same or similar agent. Sensitization and elicitation are generally mediated by immunoglobulins, primarily IgE, and the responses may range from minor palatal or skin itching and rhinitis to severe bronchial spasms and wheezing, anaphylaxis, and death. In addition to IgE responses to food allergens, IgA has been identified as an inducible immune mediator primarily in the gastrointestinal mucosa in response to foods, foreign proteins, pathogenic microorganisms, and toxins. The role of IgA in classical allergy has been investigated (Macpherson et al., 2008).

Assessment of the 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 a protein that could be a de novo allergen. Predictive animal testing for allergens in foods (GE and non-GE) is not sufficient for allergy assessment (Wal, 2015). Research efforts are ongoing to discover or develop an animal model that predicts sensitization to allergy (Ladics and Selgrade, 2009), but so far none has proved predictive (Goodman, 2015). Therefore, researchers have relied on multiple indirect methods for predicting whether an allergic response could be caused by a protein that is either added to a food by genetic engineering or appears in the 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 increase due to genetic engineering.

A flow diagram of the interactive approach to allergen testing recommended by the Codex Alimentarius Commission (CAC, 2009) and EFSA (2010, 2011a) is presented in Figure 5-3 (Wal, 2015); Box 5-2 describes the EPA testing of the *Bt* toxin Cry1F that generally follows this approach. The logic behind the approach starts with the fact that any gene for a protein that comes from a plant that is known to cause food allergies has a higher likelihood of causing allergenicity than any gene from a plant that does not cause an allergic response. If the introduced protein is similar to a protein already known to be an allergen, it becomes suspect and should be tested in people who have an allergy to the related protein. Finally, if a protein fits none of the above characteristics but is not digested by simulated gastric fluid, it could be a novel food allergen. The latter factor comes from

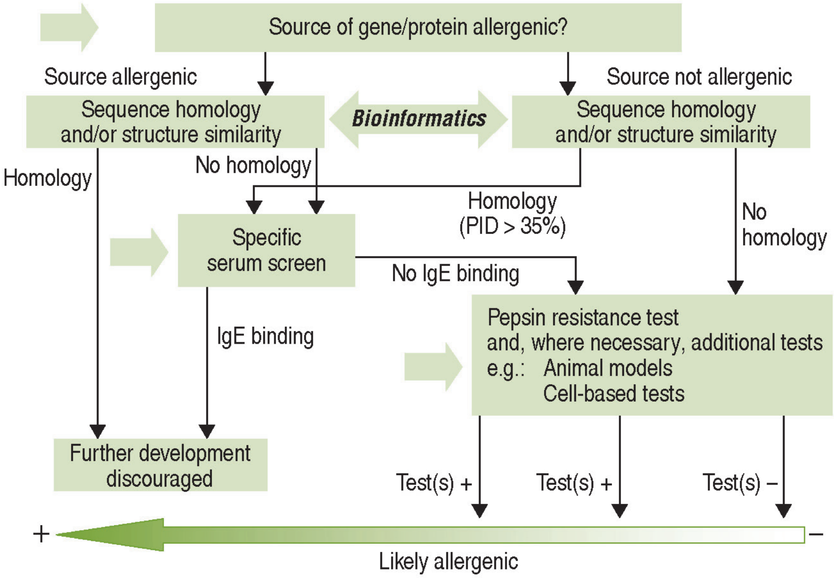

FIGURE 5-3 Flow chart summarizing the weight-of-evidence approach for assessment of allergenicity of a newly expressed protein in genetically engineered (GE) organisms.
SOURCE: CAC (2009) and EFSA (2010, 2011a) in Wal (2015).
NOTE: This approach starts with questions about the plant from which the gene originated and the sequence and the structure of the protein compared with known allergenic proteins. It then goes on to more biological testing of the protein itself. If the flow chart for the specific protein ends up in the lower left corner, the risk of allergenicity is considered too high to proceed with development of the GE crop.

research demonstrating that some, but not all, proteins already known to be food allergens are resistant to digestion by gut fluid.

There is one case in which that approach was used and a GE crop with allergenicity issues was detected early and prevented from being commercialized, and a second case in which a GE crop was withdrawn from the market based on the possibly that it included a food allergen. In the first case, research was conducted on a soybean line genetically engineered to produce a Brazil nut (*Bertholletia excelsa*) protein, which was a known allergen. Sera from patients allergic to Brazil nut protein were available and tested positive for activity against the GE soybean protein. Because the segregation from the human food supply of GE soybean with that protein could not be guaranteed, the project was halted (Nordlee et al., 1996). The soybean variety was never commercialized.

In the second case, EPA allowed a *Bt* maize variety developed by Aventis CropScience with a potential for allergenicity (due to decreased digestion of the protein Cry9c in simulated gastric fluid) to be sold as cattle feed under the name StarLink™; because of the potential for allergenicity, the variety was not approved for direct human consumption. However, the *Bt* protein was found in human food, so the maize variety was removed from all markets. After that incident, EPA no longer distinguished between *Bt* proteins in human food versus in animal feed (EPA, 2001b). *Bt* crop varieties are approved in the United States for all markets or none.

The interactive approach for testing should work for GE crops when the testing is for a transgene that is expressed by the plant as a protein that does not affect its metabolism (for example, *Bt* toxins). The testing does not cover endogenous allergens whose concentrations have been increased by unintended effects of genetic engineering. In 2013, the European Commission set a requirement for assessing endogenous allergens in GE crops (EC, 2013). A number of articles since then have supported the approach (Fernandez et al., 2013) or have found it unnecessary and impractical (Goodman et al., 2013; Graf et al., 2014). Soybean is an example of a crop that has endogenous allergens. A paper on endogenous soybean allergens concluded that there is enough knowledge of only some soybean allergens for proper testing (Ladics et al., 2014). As emphasized by Wal (2015), there is considerable variation among conventionally bred varieties in the concentrations of endogenous allergens, especially when they are grown under different conditions. Therefore, the existing variation must be taken into consideration in assessing a GE variety. Of course, the issue is not only the magnitude of variation but the potential change in the overall exposure of the global human population to the allergen.

One example of an existing potential allergen of concern is gamma-zein, one of the storage proteins produced in the maize kernel that is a comparably hard-to-digest protein (Lee and Hamaker, 2006). Concern was expressed to the committee that GE maize may have higher amounts of gamma-zein, which could be allergenic (Smith, 2014). Krishnan et al. (2010) found that young pigs consuming maize generate antibodies against gamma-zein. That observation and the fact that the protein withstands pepsin digestion suggest that gamma-zein could be an allergen. In a comparison of the *Bt* maize line MON810 with non-*Bt* maize, known maize allergens, including the 27-kDa and 50-kDa gamma-zein proteins, were not found to be in significantly different amounts (Fonseca et al., 2012). On the other hand, conventionally bred Quality Protein Maize is reported to have a 2 to 3 fold higher concentration of the 27-kDa gamma-zein protein (Wu et al., 2010). There is one patent for decreasing gamma-zein through genetic engineering.[5]

There can be a connection between immune response and allergenicity. One well-cited study brought up in the public comment period was that by Finamore et al. (2008), who assessed the effect of *Bt* maize ingestion on the mouse gut and peripheral immune system. They found that *Bt* maize produced small but statistically significant changes in percentage of T and B cells and of CD4+, CD8+, γδT, and αβT subpopulations at gut and peripheral sites and alterations of serum cytokines in weanlings fed for 30 days and in aged mice. However, there was no significant response in weaning mice that were fed for 90 days, which they related to further maturation of the immune system. They concluded that there was no evidence that the *Bt* toxin in maize caused substantial immune dysfunction. Similarly, Walsh et al. (2012a) did not find immune function changes in a long-term pig feeding study (80 or 110 days) on *Bt* MON810 maize compared with non-GE maize. Overall, no changes of concern regarding *Bt* maize feeding and altered immune response have been found.

At a public meeting that the committee held on health effects of GE foods, a question was raised about whether current testing for allergenicity is insufficient because some people do not have acidic conditions in their stomachs. Regarding that issue, digestibility of the proteins is assessed with simulated gastric fluid (0.32 percent pepsin, pH 1.2, 37°C), under the premise that an undigested protein may lead to the absorption of a novel allergenic fragment (Astwood et al., 1996; Herman et al., 2006). Stomach fluid is typically acidic, with a pH of 1.5–3.5, which is the range at which pepsin (the digestive enzyme of the stomach) is active, and the volume of stomach fluid is 20–200 mL (about 1–3 ounces). Simulated gastric fluid was developed to represent human gastric conditions in the stomach and is used in bioavailability studies of drugs and foods (U.S. Pharmacopeia, 2000).

In general, if the pH of the stomach is greater than 5, pepsin will not be active, and less breakdown of large proteins will take place. Hence, the usefulness of simulated gastric fluid in the case of a less acidic (higher pH) stomach is questionable, whether used for non-GE foods or GE foods. Untersmayr and Jensen-Jarolim (2008:1301) concluded that "alterations in the gastric milieu are frequently experienced during a lifetime either physiologically in the very young and the elderly or as a result of gastrointestinal pathologies. Additionally, acid-suppression medications are frequently used for treatment of dyspeptic disorders." Trikha et al. (2013) used a group of 4,724 children (under 18 years old) who had received a

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[5] Jung, R., W.-N. Hu, R.B. Meeley, V.J.H. Sewalt, and R. Nair. Grain quality through altered expression of seed proteins. U.S. Patent 8,546,646, filed September 14, 2012, and issued October 1, 2013.

diagnosis of gastroesophageal reflux disease (GERD) and who were treated with gastric acid-suppressive medication and matched with 4,724 children who had GERD but were not so treated. Those treated with acid-reducing medicine were more than 1.5 times as likely to have a diagnosis of food allergy as those who were not so treated. The difference between the two GERD groups was statistically significant (hazard ratio, 1.68; 95-percent confidence interval, 1.15–2.46).

The National Research Council report *Safety of Genetically Engineered Foods* pointed out that there were important limitations in allergenicity predictions that could be done before commercialization (NRC, 2004). Since that report was published, there have been improvements in the allergen database, and research has been funded to improve precommercialization prediction. However, as the committee heard from an invited speaker, "no new methods have been demonstrated to predict sensitization and allergy in the absence of proven exposure" (Goodman, 2015). Before commercialization, the general population will probably not have been exposed to an allergen similar enough to an allergen in a GE plant to cause cross-reactivity, so it would be useful to use the precommercialization tests only as a rough predictor. To ensure that allergens did not remain in the food system, the *Safety of Genetically Engineered Foods* report called for a two-step process of precommercialization testing and post-commercialization testing. Even though progress has been made on allergenicity prediction since that report was published in 2004, the committee found that post-commercialization testing would be useful in ensuring that no new allergens are introduced. There have been no steps toward post-commercialization testing since 2004. The committee recognized that such testing would be logistically challenging, as described in a scientific report to EFSA (ADAS, 2015). Post-commercialization surveillance of such specific agents as drugs and medical devices is difficult, but there is generally a well-defined endpoint to look for in patients. In the case of food, the detection of an allergic response to a particular protein would be confounded by multiple exposures in the diet. However, several region-wide human populations have been exposed to GE foods for many years whereas others have not; this could enable an a priori hypothesis to be tested that populations that have been exposed to foods from specific GE crops will not show a higher rate of allergic response to such foods.

> **FINDING: For crops with endogenous allergens, knowing the range of allergen concentrations in a broad set of crop varieties grown in a variety of environments is helpful, but it is most important to know whether adding a GE crop to the food supply will change the general exposure of humans to the allergens.**

FINDING: Because testing for allergenicity before commercialization could miss allergens to which the population had not previously been exposed, post-commercialization allergen testing would be useful in ensuring that consumers are not exposed to allergens, but such testing would be difficult to conduct.

FINDING: There is a substantial population of persons who have higher than usual stomach pH, so tests of digestibility of proteins in simulated acidic gastric fluid may not be relevant to this population.

GENETICALLY ENGINEERED CROPS AND OCCURRENCE OF DISEASES AND CHRONIC CONDITIONS

The overall results of short-term and long-term animal studies with rodents and other animals and other data on GE-food nutrient and secondary compound composition convinces many (for example, Bartholomaeus et al., 2013; Ricroch et al., 2013a,b; Van Eenennaam and Young, 2014) but not all involved researchers (for example, Dona and Arvanitoyannis, 2009; Domingo and Bordonaba, 2011; Hilbeck et al., 2015; also see DeFrancesco, 2013) that currently marketed GE foods are as safe as foods from conventionally bred crops. The committee received comments from an invited speaker (Smith, 2014) and from the public regarding the possible relationship between increases in the incidence of specific chronic diseases and the introduction of GE foods into human diets. Appendix F includes a representative list of the comments about GE food safety that were sent to the committee through the study's website. The comments mentioned concerns about such chronic diseases as cancers, diabetes, and Parkinson's; possible organ-specific injuries (liver and kidney toxicity); and such disorders as autism and allergies. Smith (2003:39) made the claim that "diabetes rose by 33 percent from 1990 to 1998, lymphatic cancers are up, and many other illnesses are on the rise. Is there a connection to [genetically modified] foods? We have no way of knowing because no one has looked for one."

As part of the committee's effort to respond to its task to "assess the evidence for purported negative effects of GE crops and their accompanying technologies," it used available peer-reviewed data and government reports to assess whether any health problems may have increased in frequency in association with commercialization of GE crops or were expected to do so on the basis of the results of toxicity studies. The committee presents additional biochemical data from animal experiments but relies mostly on epidemiological studies that used time-series data. The epidemiological data for some specific health problems are generally robust over time (for example, cancers) but are less reliable for others. The committee presents the available data knowing that they include a number of sources of bias, including changes over time in survey methods and in the tools for detection of specific chronic diseases. As imperfect as the data may be, they are in some cases the only information available beyond animal experiments for formulating or testing hypotheses about possible connections between a GE food and a specific disease. The committee points out that the lack of rigorous data on incidence of disease is not only a problem for assessing effects of GE foods on health. More rigorous data on time, location, and sociocultural trends in disease would enable better assessment of potential health problems caused by environmental factors and other products from new technologies.

Cancer Incidence

A review of the American Cancer Society's database indicates that mortality from cancers in the United States and Canada has continued to decrease or stabilized in all categories except cancers of the lung and bronchus attributable to smoking. The decreases in mortality are due in part to early detection and improved treatment, so mortality data can mask the rate at which cancers occur. For that reason, the committee sought data on cancer incidence rather than cancer mortality. Figures 5-4 and 5-5 show

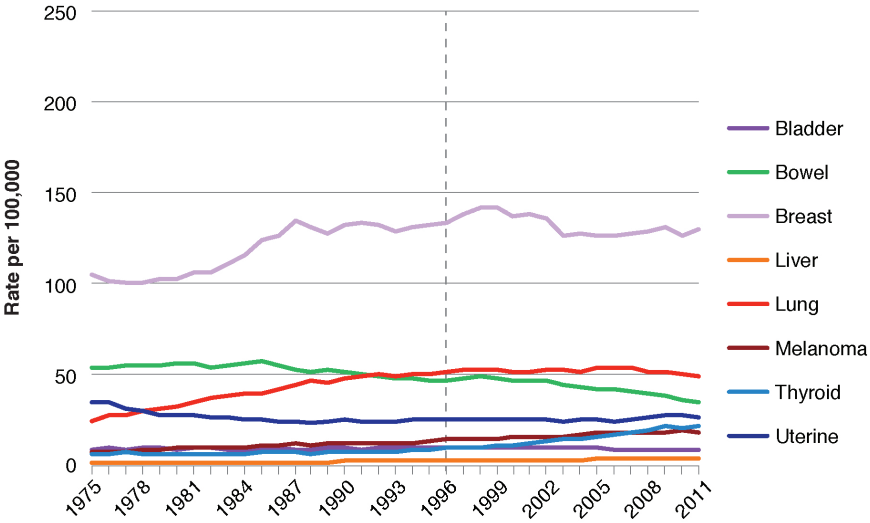

FIGURE 5-4 Trends in cancer incidence in women in the United States, 1975–2011.
SOURCE: NCI (2014).
NOTE: Age-adjusted to the 2000 U.S. standard population and adjusted for delays in reporting. Dashed line at 1996 indicates year GE soybean and maize were first grown in the United States.

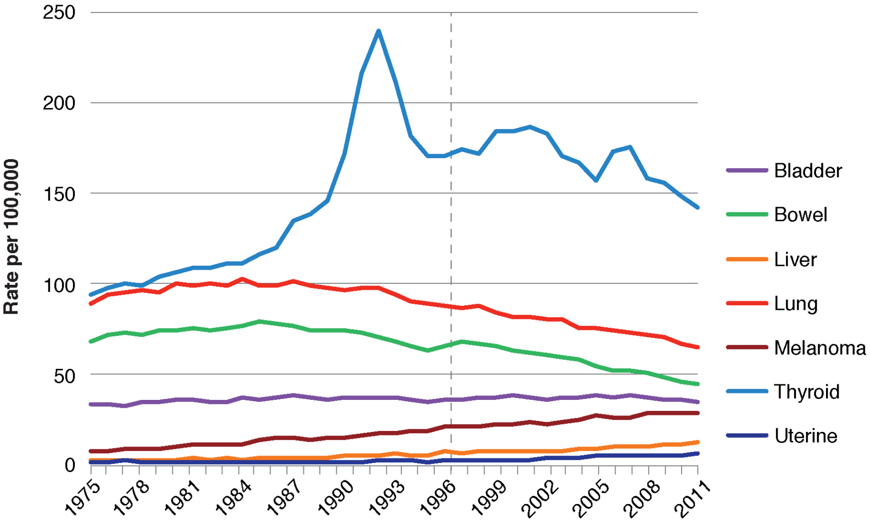

FIGURE 5-5 Trends in cancer incidence in men in the United States, 1975–2011.
SOURCE: NCI (2014).
NOTE: Age-adjusted to the 2000 U.S. standard population and adjusted for delays in reporting. Dashed line at 1996 indicates year GE soybean and maize were first grown in the United States.

changes in cancer incidence in U.S. women and men, respectively, from 1975 to 2011 (NCI, 2014). If GE foods were causing a substantial number of specific cancers, the incidence of those cancers would be expected to show a change in slope in the time series after 1996, when GE traits were first available in commercial varieties of soybean and maize. The figures show that some cancers have increased and others decreased, but there is no obvious change in the patterns since GE crops were introduced into the U.S. food system. Figures 5-6 and 5-7 show cancer incidence in women and men in the United Kingdom, where GE foods are not generally being consumed. For the specific types of cancers that are reported in both the United States and the United Kingdom, there is no obvious difference in the patterns that could be attributed to the increase in consumption of GE foods in the United States. (The absolute numbers cannot be compared because of differences in methodology.)

Forouzanfar et al. (2011) published data on breast and cervical cancer incidence worldwide from 1980 to 2010. As can be seen in Figure 5-8, the global incidence of those two cancers has increased. An examination of the plots for North America (high income) (Canada and the United States), where GE foods are eaten, compared with the plots for western

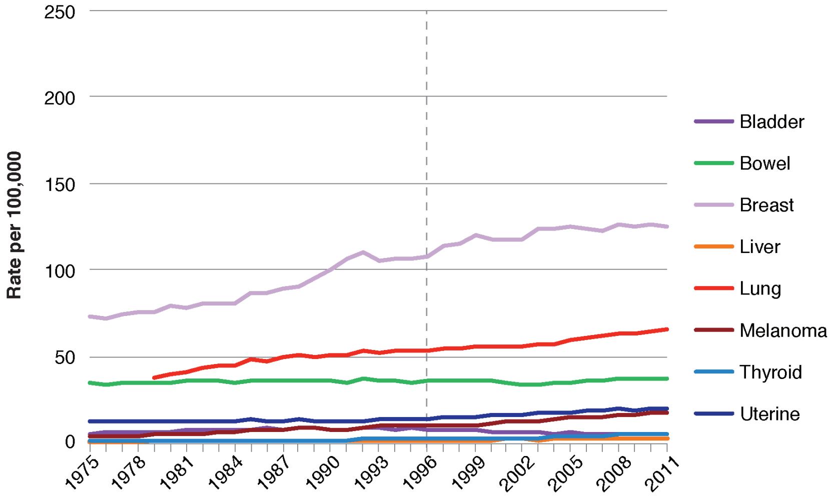

FIGURE 5-6 Cancer incidence in women in the United Kingdom, 1975–2011.
DATA SOURCE: Cancer Research UK. Available at http://www.cancerresearchuk.org/health-professional/cancer-statistics. Accessed October 30, 2015.
NOTE: Dashed line at 1996 indicates year GE soybean and maize were first grown in the United States.

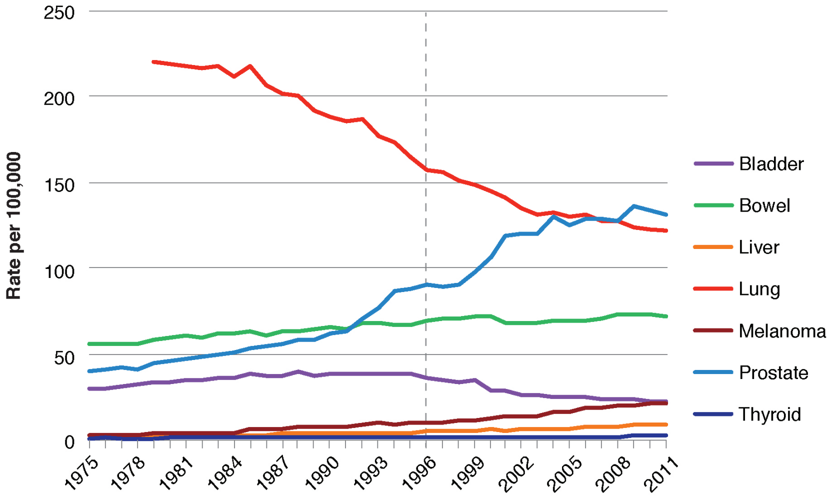

FIGURE 5-7 Cancer incidence in men in the United Kingdom, 1975–2011.
DATA SOURCE: Cancer Research UK. Available at http://www.cancerresearchuk.org/health-professional/cancer-statistics. Accessed October 30, 2015.
NOTE: Dashed line at 1996 indicates year GE soybean and maize were first grown in the United States.

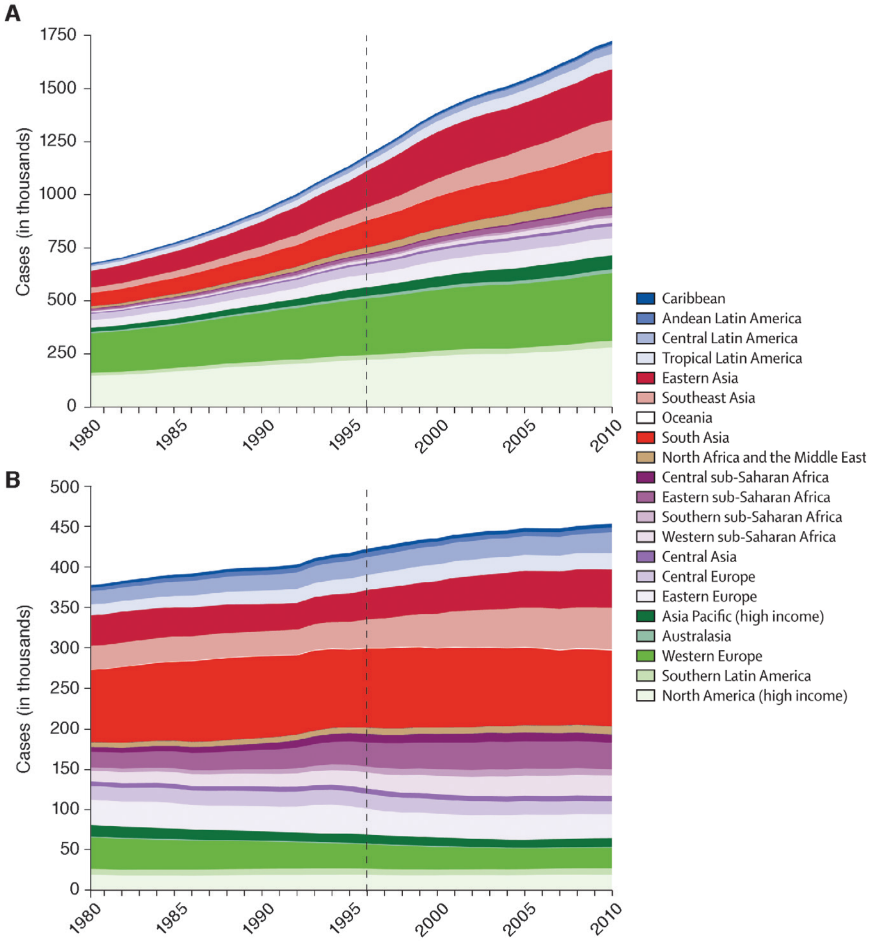

FIGURE 5-8 Global incidence of breast (A) and cervical (B) cancer.
SOURCE: Forouzanfar et al. (2011).
NOTE: North America (high income): Canada, United States; Western Europe: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom. Dashed line at 1996 indicates year genetically engineered soybean and maize were first grown in the United States.

Europe, where GE foods generally are not eaten, shows similar increases in incidence of breast cancer and no increase in cervical cancer. The data do not support the hypothesis that GE-food consumption has substantially increased breast and cervical cancer. (The data for North America [high income] and western Europe are different from those in the studies above on the incidence of cancer in the United States and the United Kingdom.)

Taken together, Figure 5 through Figure 8 do not support the hypothesis that GE foods have resulted in a substantial increase in the incidence of cancer. However, they do not establish that there is no relationship between cancer and GE foods because there can be a delay in the onset of cancer that would obscure a trend, and one could hypothesize that something else has occurred with GE foods in the United States that has lowered cancer incidence and thus obscured a relationship. The committee had limited evidence on which to make its judgments, but the evidence does not support claims that the incidence of cancers has increased because of consumption of GE foods.

There is ongoing debate about potential carcinogenicity of glyphosate in humans. Assessment of glyphosate is relevant to the committee's report because it is the principal herbicide used on HR crops (Livingston, et al. 2015), and it has been shown that there are higher residues of glyphosate in HR soybean treated with glyphosate than in non-GE soybean (Duke et al., 2003; Bøhn et al., 2014). Box 5-5 provides details about a study by Séralini et al. (2012, 2014) that concluded that glyphosate causes tumors in rats. The committee found that this study was not conclusive and used incorrect statistical analysis. The most detailed epidemiological study that tested for a relationship between cancer and glyphosate as well as other agricultural chemicals found "no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate" (Mink et al., 2012:440; also see section below "Health Effects of Farmer Exposure to Insecticides and Herbicides").

In 1985, EPA classified glyphosate as Group C (possibly carcinogenic to humans) on the basis of tumor formation in mice. However, in 1991, after reassessment of the mouse data, EPA changed the classification to Group E (evidence of noncarcinogenicity in humans) and in 2013 reaffirmed that "based on the lack of evidence of carcinogenicity in two adequate rodent carcinogenicity studies, glyphosate is not expected to pose a cancer risk to humans" (EPA, 2013:25399).

In 2015, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) issued a monograph on glyphosate as part of its volume on some organophosphate insecticides and herbicides (IARC, 2015). In the monograph, IARC classified glyphosate in Group 2A (probably carcinogenic to humans). A summary and reasons for the classification were published in *Lancet Oncology* (Guyton et al., 2015).

The 2015 IARC Working Group found that, although there is "*limited evidence* in humans for the carcinogenicity of glyphosate," there is "*sufficient evidence* in experimental animals for the carcinogenicity of glyphosate"

(IARC, 2015:78). Furthermore, IARC noted that there is mechanistic support in that glyphosate induces oxidative stress, which could cause DNA damage, and some epidemiological data that support the classification.

EFSA (2015) 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 concluded that "the level of human exposure, which determines the actual risk, was not taken into account by WHO (IARC)" (Health Canada, 2015). The Canadian agency found that current food and dermal exposure to glyphosate even by those who work directly with glyphosate is not a health concern as long as it is used as directed on product labels (Health Canada, 2015). EPA (2015) found that glyphosate does not interact with estrogen, androgen, or thyroid systems.

A comment to the committee expressed concern that glyphosate breaks down to formaldehyde, which was classified as a known human carcinogen by IARC (2006). However, this hypothesis was not supported; Franz et al. (1997) used radiolabeled glyphosate and failed to show formation of formaldehyde in the normal environmental degradation of glyphosate.

FINDING: The incidence of a variety of cancer types in the United States has changed over time, but the changes do not appear to be associated with the switch to consumption of GE foods. Furthermore, patterns of change in cancer incidence in the United States are generally similar to those in the United Kingdom and Europe, where diets contain much lower amounts of food derived from GE crops. The data do not support the assertion that cancer rates have increased because of consumption of products of GE crops.

FINDING: There is significant disagreement among expert committees on the potential harm that could be caused by the use of glyphosate on GE crops and in other applications. In determining the risk from glyphosate and formulations that include glyphosate, analyses must take into account both marginal exposure and potential harm.

Kidney Disease

It has been hypothesized that kidney disease may have increased because GE proteins reached the kidney. The committee examined epidemiological data to determine whether there was a correlation between the consumption of GE foods and the prevalence of chronic kidney disease (CKD).

The total prevalence of all stages of CKD in the United States increased 2 percent from about 12 percent in 1988–1994 to 14 percent in 1999–2004, but the total prevalence has not increased significantly since then.

Figure 5-9 presents prevalence data on the five progressively more serious, recognized stages of CKD (USRDS, 2014). The greatest percent increase is seen in Stage 3, and based on the study (USRDS, 2014), a large amount of the increase occurred in people with comorbidity of cardiovascular disease. Prevalence of CKD increases substantially with age (Coresh et al., 2003), so the aging of the U.S. population may contribute to the overall increase (U.S. Census Bureau, 2014), as does the increase in diabetes and hypertension (Coresh et al., 2007).

> **FINDING: The available data on prevalence of chronic kidney disease in the United States show a 2 percent increase from 1988 to 2004, but the increase does not appear to be attributable to consumption of GE foods.**

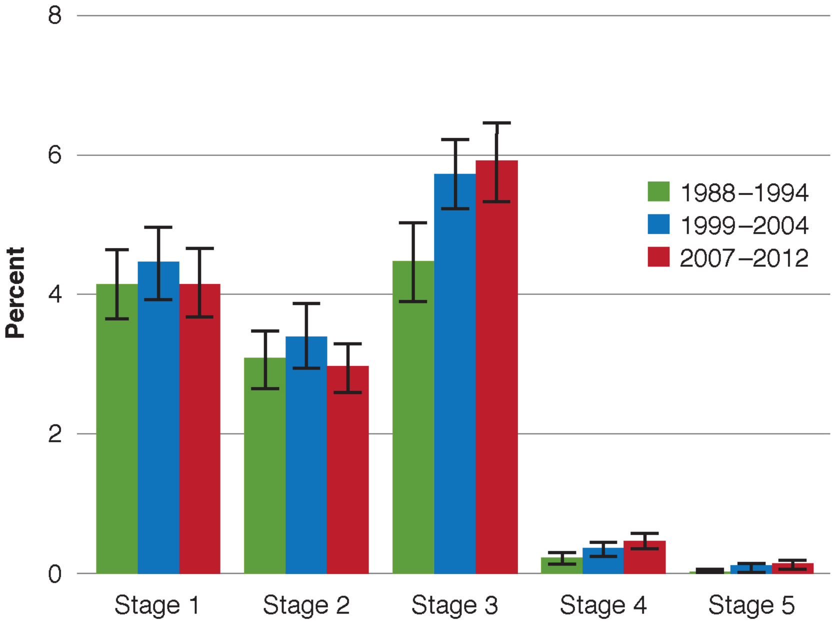

FIGURE 5-9 Prevalence of chronic kidney disease by stage among National Health and Nutrition Examination Survey (NHANES) participants, 1988–2012.
SOURCE: NHANES 1988–1994, 1999–2004, and 2005–2012; participants 20 years old and older; presented in USRDS (2014).
NOTE: Whisker lines indicate 95-percent confidence intervals.

Obesity

Obesity in humans is a complex condition associated with several genetic and environmental factors—including geography, ethnicity, socioeconomic status, lack of exercise, availability of fresh fruits and vegetables, and less nutritional meals (Thayer et al., 2012)—and an altered functioning microbiome (Turnbaugh et al., 2009).

Studies of various species examined body-weight gain when animals were fed a GE crop, a non-GE isogenic comparator, or a non-GE, nonisogenic control. The authors concluded that there were no biologically relevant differences in body-weight gain regardless of the length of the studies (Rhee et al. 2005; Hammond et al., 2006; Arjó et al., 2012; Buzoianu et al., 2012b; Ricroch et al., 2013a,b; Halle and Flachowsky, 2014; Nicolia et al. 2014).

Human population studies have shown that obesity has become more prevalent in the United States (for example, Fryar et al., 2014). An (2015) provided a graphic of the change in U.S. adults (sorted by education level) from 1984 to 2013 (Figure 5-10). As can be seen in the figure, the percentage of obese U.S. adults increased until about 2009, at which time it appears to level off. Because there is no increase in the slope after commercialization of GE crops, these data do not support the hypothesis that GE crops have increased obesity. These time-series data do not prove that there is no association, but if one is present, it is not strong.

Those statistics on obesity coincide with those on the incidence of type II diabetes in the United States (Abraham et al., 2015) and therefore do not support a relationship between GE crops and type II diabetes.

FINDING: The committee found no published evidence to support the hypothesis that the consumption of GE foods has caused higher U.S. rates of obesity or type II diabetes.

Gastrointestinal Tract Diseases

Although the gastrointestinal tract has evolved to digest dietary proteins in the stomach and small intestine effectively for absorption and use of amino acids, it is normal for some full proteins or their fragments to cross the gut barrier through a paracellular route (between cells) or damaged mucosa and for the immune system, which has a high presence at the interface of the gut wall and the internal circulation, to respond accordingly. It is also not unusual, given the high sensitivity of today's analytical equipment, for proteins or fragments to be detected in minute amounts in different body fluids. Detection methods are not specific to transgene-produced proteins but can find any dietary protein or fragment that is able to pass from the gastrointestinal tract into the bloodstream and tissues. The presence

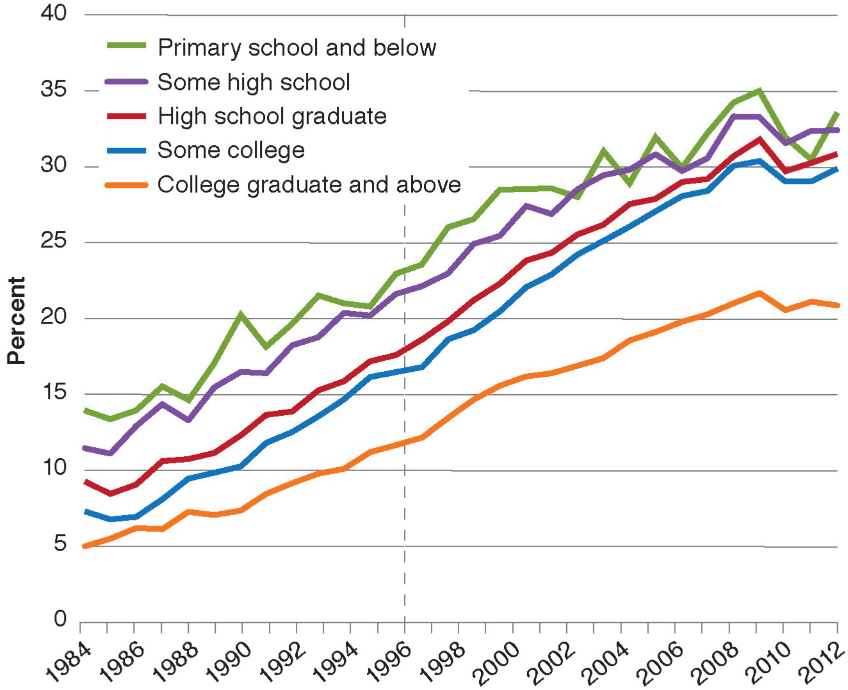

FIGURE 5-10 Annual trend for adjusted prevalence of obesity in U.S. adults by education level, 1984–2013.
SOURCE: An (2015).
NOTE: Prevalence of obesity was adjusted to account for gender, age group, and race or ethnicity. Dashed line at 1996 indicates year genetically engineered soybean and maize were first grown in the United States.

of a dietary protein or its fragment in the bloodstream or in tissues is not unusual or a cause for health concerns.

About 60–70 percent of the body's immune system is in the gastrointestinal tract's gut-associated lymphoid tissue, which has an interface with the gut luminal contents, including toxins, allergens, and the associated microbiota. For GE crops, a public concern has been that the immune system is compromised through ingested transgenic proteins. That possibility has been investigated in animal studies that examined immune system biomarkers and epithelial cell integrity (see section "Beyond Rodent Studies" above and Walsh et al., 2011).

It was suggested to the committee in presentations and public comments that fragments of transgenes may have some special properties that would result in human diseases if they were absorbed into the body through the digestive tract. The mechanism by which such genes or proteins would affect the body is not clear, although Smith (2013) hypothesized that consuming GE foods increased gut permeability.

> **FINDING: The committee could find no published evidence supporting the hypothesis that GE foods generate unique gene or protein fragments that would affect the body.**

Celiac Disease

Celiac disease is an autoimmune disorder that affects about 1 percent of the population of western countries. It is triggered in susceptible people by consumption of gluten-containing cereal grains (Fasano et al., 2003; Catassi et al., 2010). Symptoms of celiac disease are the result of an immune reaction that causes marked gastrointestinal inflammation in persons susceptible to gliadin, a component of gluten protein found in wheat, rye (*Secale cereale*), and barley (*Hordeum vulgare*) (Green and Cellier, 2007). In addition to exposure to gluten, the etiology of celiac disease is multifactorial and includes genetic predisposition, microbial infection of the gastrointestinal tract, antibiotic exposure, and gastrointestinal erosion (Riddle et al., 2012). Diagnosis is based on detection of serum concentrations (serotypes) of IgA tissue transglutaminase and endomysial antibody IgA, the relief of symptoms upon gluten avoidance, and tissue biopsy. The genetic changes related to the serotyped IgAs are found in about 30 percent of the Caucasian population, but susceptibility to celiac disease is found in only 1 percent of this population (Riddle et al., 2012).

The committee was able to find data on the incidence of celiac disease in the United Kingdom (West et al., 2014; Figure 5-11) and a detailed study conducted by the Mayo Clinic in one county in Minnesota (Murray et al., 2003; Ludvigsson et al., 2013). In the Minnesota and UK studies, there is a clear pattern of increase in celiac-disease incidence (or at least its detection or the extent of self-reports) that started before 1996 (Catassi et al., 2010), when U.S. citizens began to consume more GE foods and the use of glyphosate increased in the United States but not in the United Kingdom. The increases are similar in magnitude to that found in U.S. military personnel, in whom prevalence increased from 1.3 per 100,000 in 1999 to 6.5 per 100,000 in 2008 (Riddle et al., 2012). The authors cautioned that most cases of celiac disease are undiagnosed. Some of the observed increase may be related to improvements in diagnostic criteria, greater awareness of the disease in physicians and patients, better blood tests, and increases in the number of biopsies. However, recent observations point to an increase in incidence beyond those factors (J. A. Murray, Mayo Clinic, personal communication, February 1, 2016).

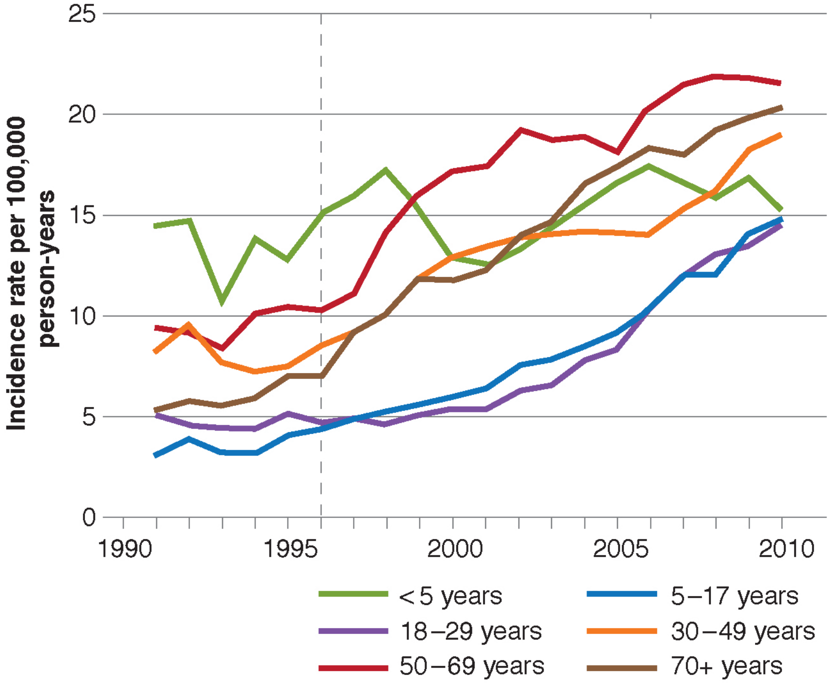

FIGURE 5-11 Three-year rolling average incidence of celiac disease in 1990–2011, by age group, in the United Kingdom.
SOURCE: West et al., 2014.
NOTE: Dashed line at 1996 indicates year genetically engineered soybean and maize were first grown in the United States.

On the basis of data collected in the 2009–2010 National Health and Nutrition Examination Survey, Rubio-Tapia et al. (2012) reported a prevalence of celiac disease of 0.71 percent with 1.01 percent in non-Hispanic whites in a sample of 7,798 subjects. It should be noted that there has not been any commercial production of GE wheat, rye, or barley in the world. The committee found no evidence that the introduction of GE foods affected the incidence or prevalence of celiac disease worldwide.

> **FINDING: Celiac-disease detection began increasing in the United States before the introduction of GE crops and the increased use of glyphosate. It appears to have increased similarly in the United Kingdom, where GE foods are not typically consumed and glyphosate use did not increase. The data are not robust, but they do not show a major difference in the rate of increase in incidence of celiac disease between the two countries.**

Food Allergies

Speakers and some members of the public suggested that the prevalence of food allergies has increased because of GE crops. The committee examined records on the prevalence of food allergies in the United States over time. As is clear from Figure 5-12 and Jackson et al. (2013), the prevalence of food allergies in the United States is rising. For a rough comparator, the committee examined data on hospital admissions for food allergies in the United Kingdom over time (Figure 5-13). UK citizens eat far less food derived from GE crops. The data (Gupta et al., 2007) suggest that food allergies are increasing in the United Kingdom at about the same rate as in the United States (but the types of measurement are different).

FINDING: The committee did not find a relationship between consumption of GE foods and the increase in prevalence of food allergies.

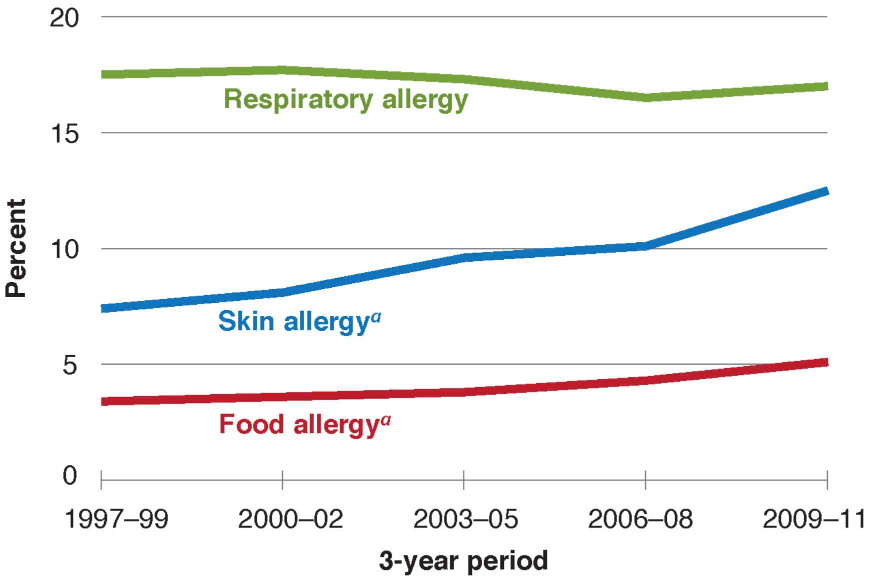

FIGURE 5-12 Percentage of children 0–17 years old in the United States with a reported allergic condition in the preceding 12 months, 1997–2011.

[a] Significantly increasing linear trend for food and skin allergy from 1997–1999 to 2009–2011.

SOURCE: Jackson et al. (2013).

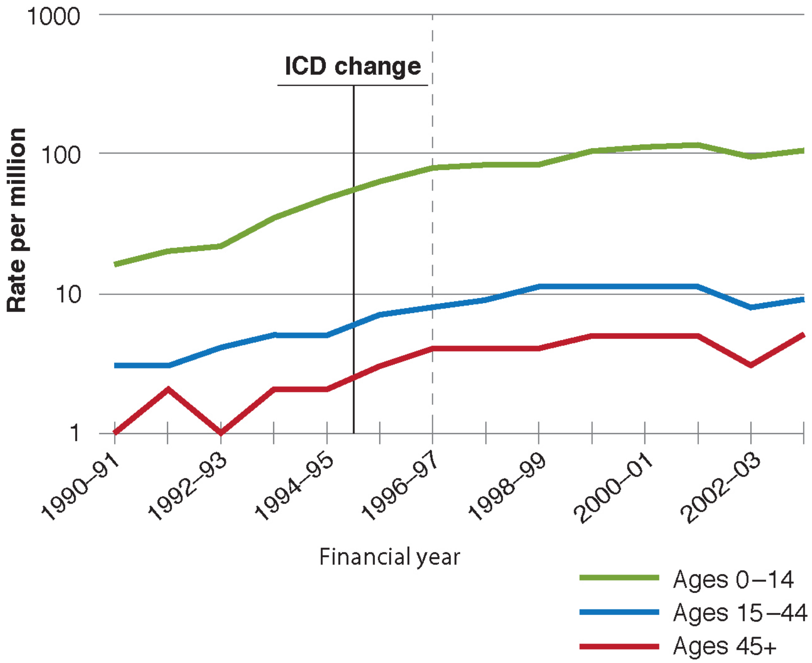

FIGURE 5-13 Trends in hospital admission rates for anaphylaxis related to food allergy by age in the United Kingdom during 1990–2004.
SOURCE: Gupta et al. (2007).
NOTES: ICD = International Classification of Diseases. Green = ages 0–14 years; blue = ages 15–44 years; red = ages 45+ years. Dashed line at 1996 indicates year genetically engineered soybean and maize were first grown in the United States.

Autism Spectrum Disorder

Autism is often described by such symptoms as difficulty in communicating, forming personal relationships, and using language and abstract concepts. According to the American Psychiatric Association (2013), autism spectrum disorder (ASD) encompasses the previous diagnoses of autism, Asperger syndrome, pervasive developmental disorder not otherwise specified, and childhood disintegrative disorder. Accurate diagnosis of ASD can be difficult, but efforts to identify children with ASD have increased in the United States over the last three decades (CDC, 2014).

In the 2010 Centers for Disease Control and Prevention (CDC) survey of ASD in 11 regions of the United States (CDC, 2014), the overall prevalence in children 8 years old was about 1 in 68 (1.47 percent), but there was wide variation among regions and sociocultural groupings of children. The CDC report stated that “the extent to which this variation might be attributable to diagnostic practices, under-recognition of ASD symptoms in some racial/ethnic groups, socioeconomic disparities in access to services, and regional differences in clinical or school-based practices that might influence the findings in this report is unclear" (CDC, 2014:1). The degree to which the increase in ASD prevalence since 1990 is due to improved diagnosis is also unclear.

Before 1990, few children in the United States or the United Kingdom had diagnoses of ASD (Taylor et al., 2013), but the prevalence has increased dramatically in both countries. Researchers in the United States and United Kingdom wrote a report that examined prevalence of ASD in the United Kingdom over time and compared it with that in the United States (Taylor et al., 2013). They concluded that "a continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical case" (Taylor et al., 2013:5). There is a higher prevalence in the United States, but it is difficult to evaluate whether it is because of differences in efforts in and approaches to diagnosis and in sociocultural factors that seem to influence prevalence. The overall similarities in prevalence of ASD in the United Kingdom, where GE foods are rarely eaten, and in the United States, where GE foods are commonly eaten, suggest that the major rise in ASD is not associated with consumption of GE foods.

> **FINDING: The similarity in patterns of increase in autism spectrum disorder in children in the United States, where GE foods are commonly eaten, and the United Kingdom, where GE foods are rarely eaten, does not support the hypothesis of a link between eating GE foods and prevalence of autism spectrum disorder.**

OTHER HUMAN HEALTH CONCERNS RELATED TO GENETICALLY ENGINEERED CROPS

The committee heard from some members of the public and some invited speakers that ailments of gastrointestinal origin could be caused by GE crops or their associated technologies or by foods derived from GE crops. The committee investigated the evidence available for that hypothesis.

Gastrointestinal Tract Microbiota

The committee received comments from the public that foods derived from GE crops could change the gut microbiota in an adverse way. Three scenarios can be considered as related to the potential effects of GE crops on the gut microbiota: the effect of the transgene product (for example, *Bt* toxin), unintended alteration of profiles of GE plant secondary metabolites, and herbicide (and adjuvant) residue (for example, glyphosate) and its metabolites in HR crops.

Research on the human gut microbiota (the community of microorganisms that live in the digestive tract) is rapidly evolving with recent reports (Dethlefsen and Relman, 2011; David et al., 2014) that suggest that microbiota perturbations occur fairly quickly owing to dietary components or antibiotic treatment. Microbiota composition and state are now well recognized to be linked to noncommunicable chronic diseases and other health problems, so factors that cause either beneficial or adverse changes in the microbiota are of interest to researchers and clinicians. However, the science has not reached the point of understanding how specific changes in microbiota composition affect health and what represents a "healthy" microbiota. The effect of different dietary patterns (for example, high-fat versus high-carbohydrate diets) on the gut microbiota has been linked to metabolic syndrome (Ley, 2010; Zhang et al., 2015).

As discussed above, most proteins, including those in GE and conventionally bred crops, are at least partially digested in the stomach by the action of pepsin that is maintained by the acidic pH of the stomach in most people. Further digestion and absorption are a function of the small intestine, where amino acids and dipeptides and tripeptides are absorbed. Therefore, an effect of a dietary protein on the microbiota, whether from GE or non-GE foods, is unlikely. However, there is some evidence that *Bt* proteins can be toxic to microorganisms (Yudina et al., 2007), and some nondegraded *Bt* protein is found within the lumen of the gut but not in the general circulation of pigs (Walsh et al., 2011). Buzoianu et al. (2012c, 2013a) studied the effect of *Bt* maize feeding on microbiota composition in pigs. In their 2012 study, 110-day feeding of *Bt* maize (variety MON810) and of isogenic non-GE maize diets led to no differences in cultured *Enterobacteriaceae, Lactobacillus*, and total anaerobes from the gut; 16S rRNA sequencing showed no differences in bacterial taxa, except the genus *Holdemania* with which no health effects are associated (Buzoianu et al., 2012c). In the follow-up study in which intestinal content of sows and their offspring were examined with 16S rRNA gene sequencing, the only observed difference for major bacterial phyla was that *Proteobacteria* were less abundant in sows fed *Bt* maize before farrowing and in offspring at weaning compared with the controls (Buzoainu et al., 2013a). Fecal *Firmicutes* were more abundant in offspring fed GE maize. There were other inconsistent differences in mostly low-abundance microorganisms. On the basis of the overall results from their studies, the authors concluded that none of the changes seen in the animals was expected to have biologically relevant health effects on the animals.

Relatively few studies have examined the influence of plant secondary metabolites from any crop on the gut microbiota. The review of Valdés et al. (2015) highlighted investigations on polyphenol-rich foods—such as red wine, tea, cocoa, and blueberries—on the microbiota. Effects were considered minor. As discussed above (see the section "Endogenous Toxins in Plants"), current commercialized GE crops do not have distinctly different secondary metabolite profiles that would lead one to think that they would affect the gut microbiota.

No studies have shown that there are perturbations of the gut microbiota of animals fed foods derived from GE crops that are of concern. However, the committee concluded that this topic has not been adequately explored. It will be important to conduct research that leads to an understanding of whether GE foods or GE foods coupled with other chemicals have biologically relevant effects on the gut microbiota.

> **FINDING: On the basis of available evidence, the committee determined that the small perturbations found in the gut microbiota of animals fed foods derived from GE crops are not expected to cause health problems. A better understanding of this subject is likely as the methods for identifying and quantifying gut microorganisms mature.**

Horizontal Gene Transfer to Gut Microorganisms or Animal Somatic Cells

Horizontal (or lateral) gene transfer is "the stable transfer of genetic material from one organism to another without reproduction or human intervention" (Keese, 2008:123). Since GE crops were commercialized, concern has been voiced by some scientists and some members of the public that foreign DNA introduced into plants through genetic-engineering technologies might, after ingestion, be transferred to the human gut microbiota and directly or indirectly (that is, from bacteria) into human somatic cells. Although most of the concern regarding horizontal gene transfer has been focused on antibiotic-resistance genes used as markers of the transgenic event, other transgenes, such as those with *Bt* toxins, have also been of concern.

A prerequisite for horizontal gene transfer is that the recombinant DNA must survive the adverse conditions of both food processing and passage through the gastrointestinal tract. Netherwood et al. (2004) showed in patients with a surgically implanted exiting tube placed at the end of the small intestine (an ileostomy) that a small amount of the GE soybean transgene EPSPS passed through the upper gastrointestinal tract to the point of the distal ileum; in subjects without an ileostomy, no transgene was recovered from their feces. In their review on stability and degradation of

DNA from foods in the gastrointestinal tract, Rizzi et al. (2012) noted that recombinant plant DNA fragments were detected in the gastrointestinal tracts of nonruminant animals but not detected in blood or other tissues, although some nonrecombinant plant DNA could be found. The authors concluded that some natural plant DNA fragments persist in the lumen of the gastrointestinal tract and in the bloodstream of animals and humans.

For an event to be considered horizontal gene transfer, DNA must be in the form of a functional (rather than fragmented) gene, enter into bacterial or somatic cells, and be incorporated into the genome with an appropriate promoter, and it must not adversely affect the competitiveness of the cells; otherwise, the effect would be short-lived.

Plant DNA has not been demonstrated to be incorporated into animal cells; however, it has been shown to be transferred in prokaryotes (bacteria). Indeed, molecular geneticists had to find genetic-engineering approaches for getting DNA to be taken into eukaryote cells and incorporated into a genome. The report *A Decade of EU-Funded GMO Research (2001–2010)* (EC, 2010a) described a study that shows that rumen ciliates (a type of microorganism) exposed to *Bt*176 maize for 2 or 3 years did not incorporate the *Bt*176 transgene. There are no reproducible examples of horizontal gene transfer of recombinant plant DNA into the human gastrointestinal microbiota or into human somatic cells. Three independent reviews of the literature on the topic (van den Eede et al., 2004; Keese, 2008; Brigulla and Wackernagel, 2010) concluded that new gene acquisition by the gut bacteria through horizontal gene transfer would be rare and does not pose a health risk.

FINDING: 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 conventionally bred crops to humans does not pose a substantial health risk.

Transfer of Transgenic Material Across the Gut Barrier into Animal Organs

Conflicting reports exist regarding the question of intact transgenes and transgenic proteins from foods crossing the gut barrier. Spisák et al. (2013) published results that indicate that complete genes in foods can pass into human blood. That is plausible, but Lusk (2014) examined the approach used by Spisák et al. and found it more likely that the findings were due to contaminants. Lusk emphasized the need for negative controls in such studies. Placental transfer of foreign DNA into mice was found by Schubbert et al. (1998) by detection in the mouse fetus, but a later report from the same laboratory (Hohlweg and Doerfler, 2001) did not find the transfer in an eight-generation study.

Studies with dairy cows and goats did not find transgenes or GE proteins in milk, although chloroplast DNA fragments were detected in milk (Phipps et al., 2003; Nemeth et al., 2004; Calsamiglia, et al., 2007; Rizzi et al., 2008; Guertler et al., 2009, Einspanier, 2013; Furgał-Dierżuk et al., 2015). That makes it clear that there is no apparent potential for trangenes or transgenic proteins to be present in dairy products. However, these animals are ruminants, and their digestive systems are different from that of humans.

Walsh et al. (2012a) studied the fate of a *Bt* gene and protein in pigs that have digestive systems that are more similar to that of humans. They found no evidence of the gene or protein in any organs or blood after 110 days of feeding on *Bt* maize, but they did find them in the digestive contents of the stomach, cecum, and colon. Fragments of Cry1Ab transgene (as well as other common maize gene fragments) but not the intact *Bt* gene were found in blood, liver, spleen, and kidney of pigs raised on *Bt* maize (Mazza et al., 2005).

FINDING: Experiments have found that Cry1Ab fragments but not intact *Bt* genes can pass into organs and that these fragments present concerns no different than other genes that are in commonly consumed non-GE foods and that pass into organs as fragments.

FINDING: There is no evidence that *Bt* transgenes or proteins have been found in the milk of ruminants. Therefore, the committee finds that there should be no exposure to *Bt* transgenes or proteins from consuming dairy products.

OVERALL FINDING ON PURPORTED ADVERSE EFFECTS ON HUMAN HEALTH OF FOODS DERIVED FROM GE CROPS: On the basis of detailed examination of comparisons of 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 human epidemiological data, the committee found no differences that implicate a higher risk to human health from GE foods than from their non-GE counterparts.

ASSESSMENT OF HUMAN HEALTH BENEFITS FROM GENETICALLY ENGINEERED CROPS

There are now a number of examples of crops, either commercialized or in the pipeline toward commercialization, that have GE traits that could improve human health. Improvement of human health can be the sole motivation for development of a specific crop trait, or it can be the secondary effect of a crop trait that is developed primarily for another reason. For example, the genetic engineering of rice to have higher beta-carotene has the specific goal of reducing vitamin A deficiency. GE maize that produces *Bt* toxins is engineered to decrease insect-pest damage, but a secondary effect could be a decrease in contamination of maize kernels by fungi that produce mycotoxins, such as fumonisins, that at high concentrations could impair human health. Beyond the direct effects of the crops on improvement of human health, there is also a potential indirect benefit associated with a decline in the exposure of insecticide applicators and their families to some insecticides because some GE plants decrease the need for insecticidal control.

Foods with Additional Nutrients or Other Healthful Qualities

Improved Micronutrient Content

According to WHO, some 250 million preschool children are vitamin A–deficient. Each year, 250,000–500,000 vitamin A–deficient children become blind, and half of them die within 12 months of losing their sight.[6] Unlike children in wealthier societies, those children have diets that are restricted mostly to poor sources of nutrients, such as rice (Hefferon, 2015). Overall improvement of the diets of the children and their parents is a goal that has not been reached; measures that improve the nutritional quality of their food sources are desirable although not optimal, as a diverse, healthy diet would be.

Crop breeders have used conventional breeding to improve the concentrations of beta-carotene in maize (Gannon et al., 2014; Lividini and Fiedler, 2015), cassava, banana and plantain (*Musa* spp.) (Saltzman et al., 2013), and sweet potato (*Ipomoea batatas*) (Hotz et al., 2012a,b). There is some loss of beta-carotene during storage and cooking, but bioavailability is still good (Sanahuja et al., 2013; De Moura et al., 2015). The most rigorous assessments of the effects of those high–beta-carotene varieties were conducted with orange-fleshed sweet potato (high in beta-carotene) in farming areas of Mozambique and Uganda. In both countries, there was increased beta-carotene intake. In Uganda, there was a positive relationship between consumption of high–beta-carotene sweet potato and positive vitamin A status (Hotz et al., 2012a). A more recent study in Mozambique found a decrease in diarrhea prevalence associated with consumption of the high–beta-carotene sweet potato (Jones and DeBrauw, 2015).

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[6] Micronutrient deficiencies. Available at http://www.who.int/nutrition/topics/vad/en/. Accessed October 30, 2015.

No reported experiments have tested any crop with high–beta-carotene for unintended effects. There has been concern about the potential for too high a concentration of beta-carotene in crops because of the hypervitaminosis A syndrome that can be caused by direct intake of too much vitamin A, but that is not a problem when the source is beta-carotene (Gannon et al., 2014).

Golden Rice, which was produced through genetic engineering to increase beta-carotene content, is one of the most recognized examples of the use of genetic-engineering technology to improve a crop's nutritional value. It is based on the understanding that rice possesses the entire machinery to synthesize beta-carotene in leaves but not in the grain. The breakthrough in the development of Golden Rice was the finding that only two genes are required to synthesize beta-carotene in the endosperm of the rice grain (Ye et al., 2000). The first version of Golden Rice had a beta-carotene content of 6 µg/g. To raise the content to a point where it could alleviate vitamin A deficiency without consumption of very large amounts of rice, a second version of Golden Rice was produced by transforming the plant with the *psy* gene from maize. The carotene content was thereby raised above 30 µg/g (Paine et al., 2005). Varieties that yield well, have good taste and cooking qualities, and cause no adverse health effects from unintended changes in the rice could have highly important health effects (Demont and Stein, 2013; Birol et al., 2015). There have been claims that Golden Rice was ready for public release for well over a decade (Hefferon, 2015), but this is not the case.

There is a publication on a field test of the first version of Golden Rice (Datta et al., 2007), but the committee could not find information on the newer, higher–beta-carotene Golden Rice in the peer-reviewed literature. Therefore, it contacted the International Rice Research Institute (IRRI) Golden Rice project coordinator, Violeta Villegas, for an update on the status of the project. In discussions with Dr. Villegas (IRRI, personal communication, 2015), it was clear that the project is progressing with a new lead transgenic event, GR2-E, because of difficulties with the previous lead event, GR2-R. The GR2-E event has been backcrossed into varieties that have been requested by several countries including the Philippines, Bangladesh, and Indonesia. As of March 2016, Golden Rice GR2-E in PSBRc82 and BRRI dhan20 genetic backgrounds was being grown in confined field tests in the Philippines and Bangladesh, respectively. Both Golden Rice varieties underwent preliminary assessment inside the greenhouse prior to planting in confined field tests. If performance is good, the varieties will be moved to open field-testing on multiple locations. Once a food regulatory approval is received in one of the participating countries, IRRI will supply the rice with the GR2-E event to an independent third party to assess its efficacy at alleviating vitamin A deficiency.

Past issues with persons and organizations opposed to Golden Rice for a myriad of reasons may have affected IRRI's work on the rice, but the overall project status[7] points out that development of Golden Rice varieties that meet the needs of farmers and consumers and that are in full compliance with the regulatory systems of the partnering countries remains the primary objective. IRRI's summary statement on its Golden Rice project was that "Golden Rice will only be made available broadly to farmers and consumers if it is successfully developed into rice varieties suitable for Asia, approved by national regulators, and shown to improve vitamin A status in community conditions. If Golden Rice is found to be safe and efficacious, a sustainable delivery program will ensure that Golden Rice is acceptable and accessible to those most in need."[8]

Increasing concentrations of beta-carotene is only one goal of conventional crop breeding and genetic engineering. Projects for increasing iron and zinc in crops as different as wheat, pearl millet (*Pennisetum glaucum*), and lentil (*Lens culinaris*) are at varied stages of development (Saltzman et al., 2013).

> **FINDING: Experimental results with non-GE crop varieties that have increased concentrations of micronutrients demonstrate that both GE and non-GE crops with these traits could have favorable effects on the health of millions of people, and projects aimed at providing these crops are at various stages of completion and testing.**

Altering Oil Composition

Substantial efforts have been made to increase the oxidative stability of soybean oil, a major cooking oil all over the world, as a means of avoiding trans-fats generated through the hydrogenation process and enhancing omega-3 fatty acid content of the oil for use in both food and feed applications. Soybean oil is composed principally of five fatty acids: palmitic acid (16:0, carbon number:double bond number), stearic acid (18:0), oleic acid (18:1), linoleic acid (18:2), and linolenic acid (18:3) in approximate percentages of 10, 4, 18, 55, and 13. High content of unsaturated fats creates a disadvantage in industrial processing because they are susceptible to oxidation and trans-fat generation during hydrogenation, whereas oils with a high percentage of oleic acid (about 80 percent) require less processing and offer another route to decrease concentrations

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[7] What is the status of the Golden Rice project coordinated by IRRI? Available at http://irri.org/golden-rice/faqs/what-is-the-status-of-the-golden-rice-project-coordinated-by-irri. Accessed October 30, 2015.

[8] *Ibid.*

of trans-fats in food products. High-oleic acid-containing soybean was produced by downregulating expression of the fatty acid desaturating enzymes FAD2-1A and -1B to decrease the concentration of trans-fats in soybean (EFSA, 2013). In 2015, high-oleic acid soybean was commercially available in North America and was produced on a small area in the United States for specialty-product contracts (C. Hazel, DuPont Pioneer, personal communication, December 14, 2015).

Canola (*Brassica napus*), known in Europe as rapeseed, is the major oilseed crop in Canada. Canola was developed through conventional breeding at the University of Manitoba, Canada, by Downey and Stefansson in the early 1970s and had a good nutritional profile—58-percent oleic acid and 36-percent polyunsaturated fatty acids—in addition to low erucic acid and a moderate concentration of saturated fatty acid (6 percent). Because of demand for saturated functional oils for the trans-fat–free market, high-lauric acid GE canola was created in 1995 through an "*Agrobacterium*-mediated transformation in which the transfer-DNA (T-DNA) contained the gene encoding the enzyme 12:0 ACP thioesterase (*bay TE*) from the California Bay tree (*Umbellularia californica*). In addition, the T-DNA contained sequences that encoded the enzyme neomycin phosphotransferase II (NPTII). The expression of NPTII activity was used as a selectable trait to screen transformed plants for the presence of the *bay TE* gene. No other translatable DNA sequences were incorporated into the plant genome" (Health Canada, 1999:1). The presence of lauric acid (12:0) in the oil allows it to be used as a replacement for other types of oils with lauric acid (for example, coconut and palm kernel oil) in such products as "confectionery coatings and fillings, margarines, spreads, shortenings, and commercial frying oils. It has also been used as a substitute for cocoa butter, lard, beef fats, palm oil, and partially or fully hydrogenated soybean, maize, cottonseed, peanut, safflower, and sunflower oils" (Health Canada, 1999:2). However, low yield and comparably poor agronomic traits have removed high-lauric acid canola from the commercial market. The long-term use of crops with altered oil content is uncertain.

> **FINDING: Crops with altered oil composition might improve human health, but this will depend on the specific alterations, how the crops yield, and how the products of the crops are used.**

Genetically Engineered Foods with Lower Concentrations of Toxins

Acrylamide is produced in starchy foods when they are cooked at high temperatures. Processing of potatoes for French fries and potato chips generates acrylamide. Toasting bread also produces acrylamide. That is viewed as a problem because the U.S. National Toxicology Program (2014) concluded that acrylamide "is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals" and causes neurological damage at high exposure. Acrylamide is produced from a chemical reaction between asparagine and a reducing sugar, so decreasing the concentration of either is expected to decrease acrylamide. A potato line was genetically engineered to have low amounts of free asparagine and in early tests had as little as 5 percent of the acrylamide compared with non-GE potatoes when cooked at high temperatures (Rommens et al., 2008).

In 2014, USDA deregulated a low-acrylamide potato produced by Simplot Plant Sciences (USDA–APHIS, 2014c) on the basis of nonplant pest status. The company also provided information to FDA. No problems were found by FDA with respect to the company's assessment of composition or safety (FDA, 2015). It should be noted that for many people reduced acrylamide in potatoes is expected to lower overall acrylamide intake substantially, but many foods contain acrylamide (FDA, 2000b, revised 2006). An FDA survey of commonly consumed foods showed French fries at seven McDonald's locations had an average acrylamide concentration of 288 parts per billion (ppb), whereas Gerber Finger Foods Biter Biscuits had 130 ppb and Wheatena Toasted Wheat Cereal had 1,057 ppb, which is much more than from fast-food French fries (FDA, 2002, revised 2006).[9] Any toasted bread is expected to be high in acrylamide. Therefore, how much low-acrylamide potato decreases total exposure depends on individual diets. Furthermore, EPA has established limits for exposure to acrylamide, and current actual exposures are generally below the limits.

Although the low-acrylamide potato is the only GE crop with a lower food-toxin concentration that has been deregulated in the United States, other GE crops with lower natural toxin concentrations are in the pipeline. Potatoes and other crops in the "deadly nightshade" family (Solanaceae, which includes tomato and eggplant) produce glycoalkaloids, some of which have human toxicity, as described above (see the section "Endogenous Toxins in Plants" in this chapter). Langkilde et al. (2012) conducted a compositional and toxicological analysis of the potatoes with lower solanine and higher chaconine. The study used Syrian golden hamsters instead of rats because the hamsters are very sensitive to the glycoalkaloids. There were some statistically significant differences, but they were considered not of biological relevance. At this point, the evidence is not sufficient to conclude that a low-glycoalkaloid potato would be healthier for humans.

Highly toxic chemicals (aflatoxins and fumonisins) are produced by *Fusarium* and *Aspergillis* fungi on the kernels of maize (Bowers et al.,

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[9] Acrylamide concentrations reported by FDA were for individual purchased food products and were not adjusted for unit-to-unit variation.

2014). Aflatoxins are considered by the U.S. National Toxicology Program (2014) to be "human carcinogens based on sufficient evidence of carcinogenicity from studies in humans." They are also associated with many other illnesses and considered a global health problem (Wild and Gong, 2010). Fumonisins cause a number of physiological disorders and are considered possibly carcinogenic to humans (IARC, 2002). Several investigators have reported a substantial decrease in fumonisins in *Bt* maize compared with conventionally bred varieties (Munkvold and Desjardins, 1997; Bowers et al., 2014). However, there is no clear association between *Bt* maize and aflatoxin concentrations (Wiatrak et al., 2005; Abbas et al., 2007; Bowen et al., 2014).

Research continues on how to use genetic engineering to develop varieties of maize and peanut (*Arachis hypogaea*) that inhibit aflatoxin production, but a GE solution has so far been elusive (Bhatnagar-Mathur et al., 2015). A reduction in aflatoxin in both maize and peanut would have substantial health benefits in some developing countries (Williams et al., 2004; Wild and Gong, 2010).

FINDING: It is possible that GE crops that would result in improved health by lowering exposure of humans to plant-produced toxins in foods could be developed, but there is insufficient information to assess the possibility. However, GE plants that indirectly or directly reduce fungal-toxin production and intake would offer substantial benefits to some of the world's poorest populations, which have the highest dietary intake of food-associated fungal toxins.

Health Effects of Farmer Exposure to Insecticides and Herbicides

Chapter 4 presents data that demonstrate substantially lower use of insecticides in some *Bt* crops than in conventionally bred crops. There is a logical expectation that a decrease in the number of insecticide applications would lead to lower farm-worker exposure and therefore lower health burden, especially in countries where acute poisonings due to applicator exposure are common. Racovita et al. (2015) reviewed five studies of *Bt* cotton in China, India, Pakistan, and South Africa that ranged from one to four growing seasons. All reported a decline in the number of insecticide applications to *Bt* versus non-*Bt* cotton. In a study in China by Huang et al. (2002), *Bt* cotton was treated with insecticides 6.6 times and non-*Bt* cotton was treated 19.8 times during the growing season. The frequency of *Bt* and non-*Bt* cotton farmers reporting poisonings were 5 percent and 22 percent, respectively in 1999, 7 percent and 29 percent in 2000, 8 percent and 12 percent in 2001. Kouser and Qaim (2011) found fewer overall insecticide treatments in a study conducted in India: 1.5 treatments of *Bt* cotton and 2.2 treatments of non-*Bt* cotton. In this study, the farmers who used *Bt* cotton reported 0.19 poisonings per season while those with conventionally bred cotton reported 1.6 poisonings. Bennett et al. (2006) studied the same types of farmers in South Africa. *Bt* cotton was not yet widely available in the beginning of the experiment, but eventually some farmers adopted *Bt* cotton and decreased spraying. The study looked at overall poisonings according to hospital records over time; there were 20 poisonings in the year before common availability of *Bt* cotton and four in a later year, when there was 60 percent adoption of *Bt* cotton.

The findings of those and other studies (for example, Huang et al., 2005; Dev and Rao, 2007; Kouser and Qaim, 2013) are in line with an expectation of a decrease in poisonings when *Bt* cotton is grown instead of non-*Bt* cotton. However, Racovita et al. (2015:15), who carefully assessed each of the studies, found many shortcomings that led them to conclude that "the link between [genetically modified] crop cultivation and a reduction in number of pesticide poisonings should be considered as still circumstantial." The shortcomings include the fact that the number of poisonings is based on farmer recall of incidents sometimes more than a year after the field season or, in the Bennett et al. (2006) study, simply based on hospital cases. Another issue was that there may have been differences in risk–avoidance behavior between farmers who did and did not plant *Bt* cotton. Finally, the studies focused on farmers, not farm workers, who do not control farm operations. Racovita et al. (2015) called for more rigorous studies that would address the shortcomings of previous studies, given the politicized nature of the use of *Bt* crops.

Farm-worker exposure to insecticides and herbicides is lower in the United States and some other developed countries than is the case for farm workers on resource-poor farms. However, there is substantial exposure, and any effects seen in the United States would be of global concern. Prospective cohort studies of health are the high benchmark of epidemiology studies, and the Agricultural Health Study (AHS) funded by the U.S. National Institute of Environmental Health Sciences used this approach to evaluate private and commercial applicators in Iowa and North Carolina. The landmark study resulted in two peer-reviewed articles on glyphosate exposure and cancer incidence (De Roos et al., 2005; Mink et al., 2012) and one on glyphosate exposure and non-cancer health outcomes (Mink et al., 2011). De Roos et al. (2005:49) concluded that "glyphosate exposure was not associated with cancer incidence overall or with most cancer subtypes we studied." The data suggested a weak association with multiple myeloma on the basis of a small number of cases, but that association was not found in a follow-up study (DeRoos et al., 2005; Mink et al., 2012). Mink et al. (2012:440) reported on the continuation of the AHS cohort study and found "no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate." Mink et al. (2011) reviewed noncancer health outcomes that included respiratory conditions, diabetes, myocardial infarction, reproductive and developmental outcomes, rheumatoid arthritis, thyroid disease, and Parkinson's disease. They reviewed cohort, case–control, and cross-sectional studies within the AHS study and found "no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease and exposure to glyphosate" (Mink et al., 2011:172).

FINDING: There is evidence that use of *Bt* cotton in developing countries is associated with reduced insecticide poisonings. However, there is a need for more rigorous survey data addressing the shortcomings of existing studies.

FINDING: A major government-sponsored prospective study of farmworker health in the United States does not show any significant increases in cancer or other health problems that are due to use of glyphosate.

ASSESSMENT OF FOOD SAFETY OF CROPS TRANSFORMED THROUGH EMERGING GENETIC-ENGINEERING TECHNOLOGIES

Increased Precision and Complexity of Genetic-Engineering Alterations

At the time that the committee wrote its report, major commercialized GE crops had been engineered by using *Agrobacterium tumefaciens*-mediated or gene gun-mediated transformation, both of which result in semirandom insertion of the transgene into the genome. Variation in expression of the transgene was routinely observed because of the specific genomic characteristics of the insertion sites. Because of that variation, there was a need to screen large numbers of transgenic plants to identify the optimal transgenic individual. Regulations in the United States require approval of each transformation event regardless of whether the transgene itself was previously approved for release in that crop. That is at least in part because of the potential for unintended effects of each insertion.

Precision genome-editing technologies now permit insertion of single or multiple genes into one targeted location in the genome and thereby eliminate variation that is due to position effects (see Chapter 7). Such precision is expected to decrease unintended effects of gene insertion, although it will not eliminate the effects of somaclonal variation (discussed in Chapter 7).

Consider, for example, the engineering of completely new metabolic pathways into a plant for nutritional enhancement. The simplest example would be a set of two genes, such as has been used to create Golden Rice to deliver precursors of vitamin A. A more complex example would be engineering of fish oils (very long-chain unsaturated fatty acids) to improve the health profile of plant oils; depending on the target species, this process has required introduction of at least of three and at most nine transgenes (Abbadi et al., 2004; Wu et al., 2005; Ruiz-Lopez et al., 2014). If each of those transgenes is integrated into the genome on a different chromosome on the basis of separate insertion events, it will require a number of generations of crosses to put them all together in one plant. If, instead, all the transgenes could be targeted at the same site on a chromosome either simultaneously or one after another, they would not segregate from each other as they were moved into elite varieties. From a food-safety perspective, engineering transgenes into a single target locus also ensures that expression of the whole pathway is preserved so that the correct end product accumulates. Emerging genetic-engineering technologies currently enable insertion of a few genes in one construct, but in the future that number may increase dramatically.

In the future, the scale of genetic-engineering alterations may go much further than just manipulating oil profiles. The committee heard from speakers about projects aimed at changing the entire photosynthetic pathway of the rice plant (Weber, 2014) to create an entirely novel crop (Zhu et al., 2010; Ruan et al., 2012). The committee also heard from researchers interested in developing cereal crops with nitrogen fixation. Those projects are discussed further in Chapter 8. Although the precision of future genetic-engineering alterations should decrease unintended effects of the process of engineering, the complexity of the changes in a plant may leave it not substantially equivalent to its non-GE counterpart.

It is also important to note that crops that use RNA interference (RNAi) were coming on the market when the committee was writing its report. EPA convened a science advisory panel to evaluate hazards that might arise from use of this genetic-engineering approach. The panel concluded that "dietary RNA is extensively degraded in the mammalian digestive system by a combination of ribonucleases (RNases) and acids that are likely to ensure that all structural forms of RNA are degraded throughout the digestive process. There is no convincing evidence that ingested [double-stranded] RNA is absorbed from the mammalian gut in a form that causes physiologically relevant adverse effects" (EPA, 2014c:14). When the committee was writing its report, deployment of dietary RNAi was a new technology. EPA's panel made a number of recommendations, including investigating factors that may affect absorption and effects of dietary double-stranded RNAs and investigating the stability of double-stranded RNA in people who manifest diseases.

FINDING: The precision of emerging genetic-engineering technologies should decrease some sources of unintended changes in the plants, thus simplifying food-safety testing. However, engineering involving major changes in metabolic pathways or insertion of multiple resistance genes will complicate the determination of food safety because changes in metabolic pathways are known to have unexpected effects on plant metabolites.

Increased Diversity of Crops To Be Engineered

The most far-ranging effects of emerging genetic-engineering technologies may be the diversity of crops that will be engineered and commercialized. Commercial GE crops at the time the committee conducted its review were mainly high-production commodity crops (maize, soybean, and cotton) engineered with trans-kingdom genes, but the applications of emerging genetic-engineering technologies are much broader: these technologies can be easily applied to any plant species that can be regenerated from tissue culture. Furthermore, the emerging technologies described in Chapter 7 can focus on any gene in which an altered nucleotide sequence results in a desired trait.

As a consequence, the committee expects a sizable increase in the number of food-producing crop species that are genetically altered. Examples of new target crops include forages (grasses and legumes), beans, pulses, a wide array of vegetables, herbs, and spices, and plants grown for flavor compounds. New traits will probably include fiber content (either increased to add more fiber or decreased to improve digestibility), altered oil profiles, decreased concentrations of antinutrients, increased or more consistent concentrations of such phytochemicals as antioxidants (for example, flavonoids) and phytoestrogens (for example, isoflavones or lignans), and increased mineral concentrations. Some of these are considered further in Chapter 8.

From a food-safety perspective, the increase in crops and traits presents a number of challenges. First is the need to develop better and more detailed baseline data on the general chemical composition and probably the transcriptomic profiles of currently marketed conventionally bred varieties of the crops (see Chapter 7). Perhaps more problematic will be designing whole-food animal-testing regimens if the food from the crop cannot be used as a major component of the test animals' diet. Maize, rice, soybean, and other grains can be added to diets at up to 30 percent without adverse effects on animal health. That is unlikely to be the case with new spices or some vegetables. It would be beneficial if new, publicly acceptable approaches for testing could be developed that do not require animal testing (NRC, 2007; Liebsch et al., 2011; Marx-Stoelting et al., 2015). Chapter 9 addresses the potential need to move to an entirely product-based approach to regulation and testing based on the novelty of a new crop or food.

FINDING: Some future GE crops will be designed to be substantially different from current crops and may not be as amenable to animal testing as currently marketed GE crops.

RECOMMENDATION: 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.

CONCLUSIONS

The committee's objective in this chapter was to examine the evidence that supports or negates specific hypotheses and claims about the risks and benefits associated with foods derived from GE crops. As acknowledged at the beginning of the chapter, understanding the health effects of any food, whether non-GE or GE, can be difficult. The properties of most plant secondary metabolites are not understood, and isolating the effects of diet on animals, including humans, is challenging. Although there are well-developed methods for assessing potential allergenicity of novel foods, these methods could miss some allergens. However, the research that has been conducted in studies with animals and on chemical composition of GE foods reveals no differences that would implicate a higher risk to human health from eating GE foods than from eating their non-GE counterparts. Long-term epidemiological studies have not directly addressed GE food consumption, but available time-series epidemiological data do not show any disease or chronic conditions in populations that correlate with consumption of GE foods. The committee could not find persuasive evidence of adverse health effects directly attributable to consumption of GE foods.

New methods to measure food composition that involve transcriptomics, proteomics, and metabolomics provide a broad, nontargeted assessment of thousands of plant RNAs, proteins, and compounds. When the methods have been used, the differences found in comparisons of GE with non-GE plants have been small relative to the naturally occurring variation found in conventionally bred crop varieties. Differences that are detected by using -omics methods do not on their own indicate a safety problem.

There is some evidence that GE insect-resistant crops have had benefits to human health by reducing insecticide poisonings and decreasing exposure to fumonisins. Several crops had been developed or were in development with GE traits designed to benefit human health; however, when the committee was writing its report, commercialized crops with health benefits had been only recently introduced and were not widely grown, so the committee could not evaluate whether they had had their intended effects.

New crops developed with the use of emerging genetic-engineering technologies were in the process of being commercialized. The precision associated with the technologies should decrease some sources of unintended changes that occur when plants are genetically engineered and thus simplify food-safety testing. However, engineering involving major changes in metabolic pathways or insertion of multiple resistance genes will complicate the determination of food safety because changes in metabolic pathways are known to have unexpected effects on plant metabolites. Therefore, publicly funded research on novel approaches for testing future products of genetic engineering is needed so that accurate testing methods will be available when the new products are ready for commercialization.

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6

Social and Economic Effects of Genetically Engineered Crops

The previous chapter discussed the difficulty of attributing changes in health outcomes directly to foods from new crop varieties, whether genetically engineered or conventionally bred. Assessing social and economic effects[1] of genetically engineered (GE) crops is similarly challenging. GE crops were introduced to farmers in rural communities with varying social structures and heterogeneous, and often complex, farming systems. Those systems vary in numerous ways, including type of crop or crops grown, production location, farm size, farmer education, level of government policy support to farms (including incentive systems for particular crops or farming practices), and availability of credit to farmers. GE crops themselves are products of an innovation system that incorporates conventional plant breeding, molecular biology, and other agricultural sciences into an embodied technology—that is, a seed or other vegetative material. The crops also have to fit into pre-existing legal systems, which include national laws and international agreements governing patents and international trade. Inventors and regulators of GE crops have had to figure out whether and how these crops fit into the existing systems.

The literature largely supports the conclusions that insect-resistant (IR) traits can reduce or abate damage caused by biotic agents and that herbicide-resistant (HR) traits tend to reduce management time and in-

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[1] A number of international treaties, including the Cartagena Protocol on Biosafety, the Convention on Biological Diversity, and the World Trade Organization use the term *socioeconomic considerations*. For clarity purposes and to maintain uniformity with previous National Research Council reports, the committee chose to use the term *social and economic effects*.

crease time available for securing off-farm income. Those two traits are parts of a portfolio of traits that may be introduced into crops. The relative magnitude of damage reduction by IR traits and effects of other GE traits will likely vary depending on the context of the technology's use. The implication of that statement is that the social and economic effects of GE traits will also vary, especially in light of the diversity of places where crops with such traits are grown and of the end users of the technology.

Any analysis must be nuanced and acknowledge that social and economic effects of GE crops will vary in time and space and among farmers and households. This chapter assesses what is known about the social and economic effects that have occurred since GE crops were introduced by pursuing a strategy that examines a broad set of individual studies and a mix of systematic reviews and meta-analyses to identify relevant issues and effects related to GE crop adoption and use.[2] The chapter first looks at social and economic effects on or near the farm pertaining to income, small-scale farmers, farmer knowledge, gender, rural communities, and the choices available to farmers with respect to seeds and practices. It then looks beyond the farm to the effects of specific GE crops related to consumer acceptance and awareness of food derived from GE crops in the marketplace, issues related to trade, costs and benefits associated with innovation and regulatory, intellectual-property issues, and food security.

Some aspects of social and economic effects related to GE crops have been studied in more depth than others. The committee decided that, even though there was less available literature on some topics such as gender and farmer knowledge, it was still important to review and present this information in its report. The chapter focuses its attention on evidence not covered in previous reports by the National Academies of Sciences, Engineering, and Medicine.

SOCIAL AND ECONOMIC EFFECTS ON OR NEAR THE FARM

This section begins with a review of GE crops' effects on farmer incomes. The outcomes of such assessments can be affected by spatial and temporal differences; farmer, household, and consumer diversity; statistical and

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[2] The committee did not pursue a systematic review of all the literature available in all major languages. Such an approach would have required an extraordinary amount of time and financial resources that were beyond the committee's capability. That approach was pursued by a European Union project, "GMO Risk Assessment and Communication of Evidence" (GRACE, 2012–2015, available at http://cordis.europa.eu/project/rcn/104334_en.html, accessed May 9, 2016). It took 3 years to complete the search protocol and the literature review but did not complete the analysis (see Garcia-Yi et al., 2014). To review social and economic effects on or near the farm, the committee reviewed over 140 studies published between 2010 and March 2016 that were not covered in systematic reviews and formal meta-analyses.

sampling biases; and survey methods (Smale et al., 2009; Klümper and Qaim, 2014). Therefore, it is expected that the effects observed will include a variety of benefits, costs, and risks. After the review, the committee looks at the relationship between genetic-engineering technology and other dimensions at the farm level, such as gender, community, and farmer knowledge.

Income Effects

Agronomic effects such as changes in yield and insecticide and herbicide applications for GE crops with IR or HR traits, respectively, were discussed in Chapter 4. In addition to an agronomic effect, a farmer may also experience an economic effect from an increase or decrease in yield or changes in the amount of money or time spent on applying herbicides or insecticides. Most of the evidence presented in the literature on the effects of GE crops on income usually refers to changes in gross margins, which is the difference between gross income and variable costs.[3] Changes in gross margins can affect whole-farm income, household income, or both. Changes in gross margins cannot be used to extrapolate or to draw definitive conclusions about whole-farm or household income because, in most situations, whole-farm and household incomes may be sourced from on-farm and off-farm activities. The report uses the term *income effects* to capture the effects on any of the income components, with the proviso that the usage will be flexible.

There is no way to know in advance whether statistical bias and uncontrolled confounding variables may raise problems or how great the problems may be. However, knowing that it is possible for them to raise problems in studies of early adoption, Smale et al. (2009) and Smale (2012) strongly recommended that testing for these issues become standard operating procedure. The committee believes that there is no way to determine whether or to what extent studies conducted in the first decade of GE crop adoption have been affected by uncontrolled confounding variables and biases. It is necessary to revisit those studies, if possible, to test them quantitatively. More recent studies have explicitly considered these issues and have used methods to attempt to correct for biases and uncontrolled confounding variables.

At the time the committee was writing its report, few assessments of income effects had been conducted on such traits as virus resistance or drought tolerance or on quality traits that had only been on the market for a short time (such as nonbrowning of the flesh of potatoes and apples or high oleic acid in soybean). The following review concentrates on the effects of IR and HR traits.

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[3] For definitions of income-related terms such as *gross income*, *gross margin*, *household income*, *net farm income*, *net return*, *profit*, and *revenue*, see the report's glossary (Appendix G).

Economic Assessments of Genetically Engineered Crops in General

Systematic reviews and formal meta-analyses of the performance of GE crops (Raney, 2006; Qaim, 2009; Smale et al., 2009; Tripp, 2009b; Finger et al., 2011; Sexton and Zilberman, 2012; Areal et al., 2013; Mannion and Morse, 2013; Klümper and Qaim, 2014; Racovita et al., 2015) have consistently shown reductions in yield damage by insects, reductions in insecticide applications for target insect pests, decreases in management time and increases in flexibility related to HR crops, increases in gross (in some cases net) margins due to the adoption of GE crops, or combinations of all the above.

It is necessary, however, to contextualize the results because they do not imply that every farmer or group of farmers (whether adopting or not) gained from the introduction of GE crops. Other literature reviews have focused on the limitations of research and critiques of methods (Smale et al., 2009; Glover 2010). In some cases, the literature focuses on the assessments of *Bt* cotton (*Gossypium hirsutum*) grown in China and India, whereas the literature on *Bt* maize (*Zea mays*), HR maize, HR soybean (*Glycine max*), crops with both HR and IR traits, and less widely grown GE crops, such as canola (*Brassica napus*) or sugar beet (*Beta vulgaris*), is much less extensive.[4] Finally, one needs to address the issue of uncontrolled confounding variables, biases, and other methodological limitations that field researchers face in defining adoption and effects of GE crops, especially during the first decade of adoption and in places where researchers have binding restrictions to research such as access to data or inadequate funding (Boxes 6-1 and 6-2; Smale et al. 2009; Smale, 2012).

Klümper and Qaim (2014) analyzed findings of 147 studies of HR soybean, maize, and cotton and *Bt* maize and cotton in 19 countries.[5] They found that profit increased by an average of 69 percent for adopters of those crops, largely because of increased yields (21.5 percent) and decreased insecticide costs (39 percent). Another meta-analysis of findings of studies of the same crops in 16 countries[6] reported that production costs were greater for GE varieties than for non-GE varieties but that gross margins were higher on the average for the GE varieties, in large part because of their greater yields (Areal et al., 2013). Raney (2006) reviewed studies con-

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[4] For example, of the 147 studies in Klümper and Qaim (2014), 49 focused on *Bt* cotton in India and 12 were of *Bt* cotton in China.

[5] Klümper and Qaim (2014) included ex-ante and ex-post studies conducted in Argentina, Australia, Brazil, Burkina Faso, Canada, Chile, China, Colombia, Czech Republic, Germany, India, Mali, Pakistan, Philippines, Portugal, Romania, South Africa, Spain, and the United States.

[6] Areal et al. (2013) included ex-ante and ex-post studies conducted in Argentina, Australia, Canada, Chile, China, Czech Republic, France, India, Mexico, Mozambique, Philippines, Portugal, Romania, South Africa, Spain, and the United States.

BOX 6-1
Social and Economic Comparisons of Genetically Engineered and Conventionally Bred Crops: Issues and Limitations

An analysis of the literature was conducted by Smale et al. (2009) and Smale (2012), which described the issues and limitations faced by researchers of social and economic effects in developing and, to a degree, developed countries. The issues pertain particularly to studies conducted during the first decade of adoption of genetically engineered (GE) crops (1996–2006). Most researchers working in this sphere, however, are likely to encounter those issues when assessing the effects of early adoption of genetic engineering and other technologies.

Researchers conducting field work—especially in developing countries—were constrained by the lack of advanced methods and budgets. The consequence of this environment is that most studies were ad hoc and used relatively small samples that reflected how early in the adoption process they were conducted. In addition, the early studies conducted in the first decade of adoption suffered from selection and measurement bias. There are five main types of bias:

Placement bias: Initial technology-deployment programs tend to select unique farmers. The farmers may be more efficient than other farmers or may have unique characteristics that encourages participation.

Measurement bias: This bias is common in quantitative surveys and is more prevalent under binding budget constraints. In many instances in the early literature, farmer recall was used to elicit information about pressure from insect pests, insecticide and other input use, and effects on health. Farmer recall is notoriously unreliable. Alternative approaches to measuring insecticide and other input use are needed. Even determining whether a farmer is planting a GE crop or what the level of expression of an insecticidal protein is poses a challenge, especially in countries where spurious or pirated seeds have been sold. Labor input has also been notoriously difficult to measure. As Smale (2012:117) noted "as is true in any survey research, sampling error of small samples is traded for measurement error in larger surveys."

Self-selection bias: In this type of bias, farmers "self-select" into the "adopting" or "nonadopting" category. They are not assigned randomly to a specific control or treatment category. They may self-select because they have more access to information or other institutional assets such as access to seed or credit. Unobserved characteristics are not captured in systematic surveys when farmers self-select.

Simultaneity bias: Decisions about such issues as seed adoption choice and inputs are made simultaneously by farmers. Unobserved variables may affect both kinds of decisions, so estimates attempting to separate individual input choices made by farmers may be confounded. As Fernandez-Cornejo et al. (2005), Fernandez-Cornejo and Wechsler (2012), and others have shown, this confounding of the issue is relevant to the statistical validity of estimates.

continued

BOX 6-1 Continued

Omitted-variable bias: Many economically important variables are unobserved, for example, ability, productivity, lowest price to sell a good or highest price to purchase a product, or lowest wage at which a person is willing to take on work. In many cases, unobserved characteristics are correlated with the "treatment" of explanatory variables of interest. Some types of panel data methods can be used to control for some types of omitted variables.

Those kinds of bias constitute a type of uncontrolled confounding variable that implies that an outcome of a regression or statistical approach may be affected through two distinct effects: biased coefficients that may have an incorrect magnitude or sign and biased standard errors, which will affect efficiency and lead to incorrect inferences with regard to hypothesis-testing. That is, the differences between GE and conventionally bred crops may be overestimated or underestimated, or it may be concluded that the differences are statistically significant when they are not.

ducted in Argentina, China, India, Mexico, and South Africa and concluded that GE cotton, maize, and soybean provide economic gains to adopting farmers in these countries; however, the effect was highly variable and depended on national institutional capacity to help poorer farmers to gain access to suitable innovations.

Economic Assessment of Insect-Resistant Traits

Klümper and Qaim (2014) analyzed the economic benefits of IR crops separately from HR crops, but they did not separate *Bt* maize from *Bt* cotton. They found that profit increased by an average of 69 percent for adopters of the crops, largely because of increased yields (25 percent) and decreased insecticide costs (43 percent). Most of the IR studies that they reviewed were of *Bt* cotton planted in India and China. Areal et al. (2013) examined *Bt* maize and *Bt* cotton separately. Differences in production costs and yield were statistically significant in most cases. Production costs for *Bt* cotton were €13/hectare higher than those for non-GE varieties, but gross margins were larger. Production costs for *Bt* maize were also higher, €14/hectare more than for non-GE varieties. Areal and colleagues also found that gross margins were higher for *Bt* maize producers. It should also be noted, on the basis of the findings in Chapter 4, that the yield differences between *Bt* crops and the non-*Bt* counterparts may have been due to the effect of the *Bt* trait, to enhancement of yield potential of *Bt*

BOX 6-2
Testing and Correcting for Uncontrolled Confounding Variables in Studies of Adoption and Impact of Genetically Engineered Crops

Uncontrolled confounding variables are important in statistics and econometrics. Uncontrolled confounding variables introduce bias to statistical estimates. Biases may affect coefficients and their signs. Biased coefficients may lead to incorrect magnitudes or signs, and biased standard errors may affect efficiency and so lead to incorrect inferences with regard to hypothesis-testing.

In the social and economics disciplines, practitioners do not usually have the luxury of a controlled experiment. In most cases, they must rely on surveys or a set of qualitative approaches to examine adoption and use. Using those approaches, the researcher may not be able to compare results from a specific study to a baseline or to a counterfactual (for example, what would have occurred without the technology). Several methods attempt to deal with uncontrolled confounding variables and biases. Some are related to the sampling strategy used, others to the analysis. In general, methods tend to mimic one or more of the characteristics of an “ideal” experiment. An ideal experiment is one in which participants are assigned to the control and treatment groups at random, there is no self-selection (persons cannot choose to become part of the control or treatment group), a baseline is established and changes in behavior are observed before and after treatment, observations extend over a long period so that effects can be examined, and outcomes are measured correctly.

Statistical approaches used to address bias in primary data (for example, data collected directly from farmers) or secondary data (for example, data from existing databases) include Hausman, instrumental variables, generalized least squares with fixed or random effects, two-stage least squares, and control-treatment models.

Other mathematical approaches attempt to identify persons that are similar in most explanatory variables (controlling for other variables) except in the use of the technology. These “quasi-experiment” approaches attempt to mimic a randomized trial, in which farmers with as many similar characteristics as possible (for example, parity in income and education or similar patterns of input use) are assigned a treatment group (for example, adoption of genetically engineered [GE] seed) or a control group (nonadoption of GE seed). The quasi-experiments approaches include difference-in-difference, panel studies, propensity scoring matching, and nonequivalent control-group designs. They usually—but not always—require many observations to identify and pair control and treatment members.

A final type of approach is the application of randomized control trials to answer a social or economics question. Treatments and controls are assigned randomly to farmers, and measurements are collected to examine effects. This approach has grown lately in popularity in the economics literature.

varieties owing to conventional breeding, or to a combination of the two. Differences in resources and productivity between farmers who did and did not grow the *Bt* varieties could also have contributed to differences in crop performance.

Finger et al. (2011) analyzed studies of *Bt* cotton from seven countries; most of the data were from India, South Africa, China, and the United States. They also included data on *Bt* maize in 10 countries; most of the studies were conducted in Germany, Spain, South Africa, and Argentina (Finger et al., 2011). They reported that gross margins for *Bt* cotton were not different for non-GE cotton in India and South Africa. In China, the adoption of *Bt* cotton saved expenditures on insecticides and labor but did not increase yields or gross margins. U.S. adoption of *Bt* cotton could not be explained by lower insecticide costs inasmuch as U.S. farmers had alternative insect-control options available to them. The authors hypothesized that nonmonetary effects may provide a better explanation of the use of *Bt* cotton in the United States in spite of lower gross margins.

For maize, gross margins were not different for farmers using *Bt* varieties than non-GE varieties in Spain, South Africa, and Argentina. Insecticide costs were also significantly lower for Spain and Germany, which was the main reason for adoption of *Bt* maize by German farmers, in addition to better insect-pest control. Management and labor-cost information was either unavailable or not significant.

Finger et al. (2011) emphasized the heterogeneity of the data that they examined. The effects related to income (for example, yield, labor expenses, and insecticide costs) for *Bt* cotton varied widely between countries included in the survey, and they observed that the heterogeneity increased when data were analyzed at the regional level. Regional variation within countries was also apparent in the analysis of *Bt* maize studies.

Bt *Cotton.* Cotton farmers in China started adopting *Bt* varieties in the 1990s. Huang and colleagues have conducted multiple in-depth surveys there since 1999 (Pray et al., 2001; Huang et al., 2002a,b,c, 2003, 2004). Evidence presented in their studies suggests that the experience with *Bt* cotton in China has been sustained and widespread. Adoption of *Bt* cotton in China has had favorable effects on farm profits, insecticide use, health, and the environment. Pray et al. (2011) reported previously unpublished findings from China on net revenue from *Bt* cotton versus non-*Bt* cotton for 2004, 2006, and 2007. Revenue was slightly higher from *Bt* cotton than from non-*Bt* cotton in 2004 and 2006 but roughly 40 percent higher in 2007. However, the 2006 and 2007 results were not robust: only 14 and 4 farmers, respectively, who were surveyed reported growing non-*Bt* cotton in those years. Other authors have raised issues related to regional variations in benefits accruing to farmers that were due to variations in variety performance, insect-pest pressures, farmers' practices, and seed quality (Fok et al., 2005; Pemsl et al., 2005; Yang et al., 2005; Xu et al., 2008). Fok et al. (2005), for example, provided evidence of the favorable effects of *Bt* cotton adoption in the Yellow River region, but adoption has not been as successful in the Yangtze River Valley. Insect-pest pressures were lower in the Yangtze River Valley than in the Yellow River region, and the cotton varieties deployed seem to be less adapted to agroclimatic conditions.

Those results can be examined in light of longer-term studies. Qiao (2015) looked at country-wide data from before the adoption of *Bt* cotton in China in 1997 to 2012, using quantitative methods to correct for bias in input costs and labor use. The author reported that increased seed costs had been more than offset by reductions in expenditures on insecticides, reductions in labor costs, and increases in yields but that there was variability in space and time. The author estimated that the economic benefit of *Bt* cotton because of reductions in yield damage from bollworm (*Helicoverpa armigera*) and reductions in insecticide use and labor amounted to 33 billion yuan over 15 years.

Huang et al. (2010) used farm-level data collected in 1999–2007 on 16 villages in four provinces of China. The stratified random sample included information from 525 households that planted *Bt* cotton, non-*Bt* cotton, or both on 3,576 plots of land. The quantitative assessment controlled for biases by pursuing an approach that separates the effect of *Bt* cotton adoption from that of insecticide use to control the targeted insect pest; results of the quantitative assessment were thus adjusted for biases. Study results showed that the targeted insect pest (bollworm) had declined over the 10-year period in the area surveyed. Furthermore, the authors provided evidence that suppression of bollworm populations had benefited farmers of *Bt* and non-*Bt* cotton and that insecticide application rates continued to decrease over the period studied.

Bt cotton has been grown in some parts of India since 2002. Romeu-Dalmau et al. (2015) compared *Bt* cotton *Gossypium hirsutum* L. with non-*Bt* cotton *G. arboreum* under rain-fed conditions in Maharashtra, India, using interviews with 36 farmers who had less than 5 hectares of land. *G. arboretum* had been grown commonly in India before *G. hirsutum*, a species commonly grown in the United States, was introduced in the 1980s. The authors found that farmers growing *Bt G. hirsutum* spent more money than growers of *G. arboretum* on insecticides, fertilizers, seeds, and harvesting. Although yields for *Bt G. hirsutum* were greater, those farmers did not take in substantially higher revenue. In fact, farmers of *G. arboretum* received a higher market price for their cotton than did farmers of *Bt G. hirsutum*. The authors suspected that *G. arboretum* commanded a premium price because it was scarce (less than 3 percent of the cotton area in India). Overall, they found that the net revenue was not statistically different between the two varieties but that the net revenue for farmers of *Bt G. hirsutum* was less variable. However, the small number of interviews and observations (36) and the number of treatments (*Bt* versus non-*Bt*, irrigation versus non-irrigation, and *G. hirsutum* versus *G. arboretum*) limit the generalizability of the results of the study.

Kathage and Qaim (2012) conducted a set of four surveys with a panel of Indian cotton farmers in 2002–2008. Surveys included farmers in 63 villages in 10 districts of southern India (Maharashtra, Karnataka, Andhra Pradesh, and Tamil Nadu). A total of 533 farm households were included, but only 198 participated in all the surveys, so the analysis used an estimation approach for an unbalanced panel. The authors controlled for nonrandom selection bias related to technology adoption. Results showed that *Bt* cotton adoption increased yield by 24 percent and improved cotton profits by 50 percent. The results also provided evidence that adoption of *Bt* cotton raised household consumption expenditures (a proxy for household living standards) by 18 percent during 2006–2008.

In a summary report on GE crops in the United States, Fernandez-Cornejo et al. (2014) recounted that net returns were reported to have increased for adopters of *Bt* cotton in all seven studies that they examined (which were published between 1997 and 2007). Gardner et al. (2009) found evidence that *Bt* cotton provides household labor savings, but the evidence was not robust. Luttrell and Jackson (2012) did not conduct an economic analysis of *Bt* cotton versus non-GE cotton for U.S. farmers. However, they concluded that farmers in 2008 perceived benefits of planting *Bt* cotton even though many of them still had to spray for bollworm (*Helicoverpa zea* [Boddie]). Bollworm was less susceptible to Cry1Ac and Cry2Ab2 than was tobacco budworm (*Heliothis virescens* [F.]), but the protection that the *Bt* toxins provided against tobacco budworm appeared to be worthwhile to U.S. cotton farmers inasmuch as more than 75 percent of all U.S. cotton planted was *Bt* varieties in 2008. That was the case despite farmers' expressed concern about the expense of insecticide on top of the technology fee for the *Bt* traits.

Bt *Maize*. In a review of six U.S. studies of *Bt* maize, Fernandez-Cornejo et al. (2014) reported variable outcomes on net returns to adopters of *Bt* maize. Net returns increased in one study, decreased in one, and depended on the extent of targeted insect-pest infestation in the other four. The studies were published in 1998–2004. The findings of Gardner et al. (2009) on household labor savings were in line with the results of studies covered by Fernandez-Cornejo et al. Gardner and colleagues found that *Bt* maize did not provide any savings to household labor. That result was not unexpected inasmuch as it had previously been reported that many U.S. farmers do not conduct alternative forms of control for European corn borer (*Ostrinia nubilalis*); using *Bt* maize targeted for that insect pest does not replace an action that they would take otherwise.

In a province in the Philippines during the 2010 wet season, Afidchao et al. (2014) found that fertilizer costs were higher for *Bt* maize than for non-GE maize and that there was no difference in insecticide expenditures between the two varieties. The authors concluded that *Bt* maize needed more fertilizer to promote the production of the *Bt* toxin and that farmers' concerns about insect pests other than Asian corn borer (*Ostrinia furnacalis* [Guenée]) caused them to continue to spray insecticides even when *Bt* maize was planted. Average net income and return on investment did not differ between non-GE growers and *Bt* growers.

In four provinces in the Philippines in the wet season of 2004–2005, Gonzales et al. (2009) reported that, on the basis of the average yield of each province, *Bt* maize was equivalent to conventionally bred hybrids in cost efficiency. *Bt* maize was more cost-efficient than conventionally bred hybrids in the dry season of 2004–2005. In the wet season of 2007–2008, *Bt* maize was slightly more cost efficient than conventionally bred hybrids in four provinces on which there were data.[7] The same was true for the dry season of that year, although in two of the provinces cost efficiency had decreased since 2004–2005. In the wet season of 2004–2005, net income in the four provinces reporting data was 5 percent higher for *Bt* maize growers than for non-GE growers on the basis of average yield; in the dry season, it was 48 percent higher. Three years later, net income was 7 percent higher for *Bt* producers in the wet season and 5 percent higher in the dry season. The findings may have been limited by the authors' use of aggregated (official) statistics, which may not give a sense of outcome variability for yields and cost efficiency. Thus, this estimate can be seen as rough estimate of gains from *Bt* maize adoption in the country.

Bt *Eggplant.* *Bt* eggplant (*Solanum melongena*) was first planted commercially by 20 farmers in Bangladesh in 2014, so no farm-level analysis was available to the committee when it was writing its report in 2015. However, ex ante studies[8] have been performed in Bangladesh, India, and the Philippines to anticipate economic effects if *Bt* eggplant were adopted. The committee felt it was important to include the results, recognizing that the studies are best estimates and not guaranteed outcomes.

Islam and Norton (2007) conducted an ex ante study of economic effects on *Bt* eggplant farmers in Bangladesh. They surveyed 60 farmers, 30 in each of two regions, for information on input costs, crop varieties, seed

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[7] Three of the four provinces were the same as those reporting in 2004–2005.

[8] *Ex ante* means "before the event." Ex ante studies are conducted to estimate the potential effects of a change event, such as a new technology, before its introduction.

sources, losses due to eggplant fruit and shoot borer (*Leucinodes orbonalis*), and crop yields. They obtained information on expected changes in yield and variable costs from scientists and more information on preferred varieties, seed sources, losses due to eggplant fruit and shoot borer, and expected extent of *Bt* eggplant adoption from industry experts. On the basis of the data collected, the authors assumed that insecticide costs would decrease by 70–90 percent and seed, fertilizer, and harvesting costs would increase slightly. Yield was expected to increase by 30 percent. They projected that the increase in gross margins of *Bt* eggplant over non-*Bt* eggplant would be 46.5 percent in one of the surveyed regions, 40.7 percent in the other region, and 44.8 percent throughout Bangladesh. The results from their study in Bangladesh are qualitatively similar to those obtained by Francisco et al. (2012) for the potential use of *Bt* eggplant in the Philippines.

Krishna and Qaim (2008) also conducted an ex ante study of the economic effect of *Bt* eggplant, although theirs was conducted in India. They surveyed 360 eggplant farmers in 2005 in areas of India that accounted for 42 percent of eggplant production. The farmers reported that average gross margins were 66,106 rupees/hectare in one region and 24,230 rupees/hectare in another region. The farmers reported average revenue losses of 27,778 rupees/hectare to eggplant fruit and shoot borer in the season before the survey. On the basis of field trials of *Bt* eggplant but accounting for expected lower yields on farms than in field trials, Krishna and Qaim (2008) assumed that insecticide use against eggplant fruit and shoot borer would drop by 75 percent, thereby decreasing the amount spent on insecticides. Seed costs and harvesting costs were expected to increase but so was yield of marketable fruit. The overall economic result for farmer gross margins would be a 61-percent increase to 106,351 rupees/hectare in one region and a 182-percent increase to 68,269 rupees/hectare in the other region.[9]

Economic Assessment of Herbicide-Resistant Traits

Much less information is available on crops with HR traits than on those with IR traits. Finger et al. (2011) did not include HR soybean or canola in their meta-analysis because they did not identify enough studies for statistical analysis. Of 99 studies included in the Fischer et al. (2015) review of social and economic effects of GE crops, only 20 focused on HR crops. According to Areal et al. (2013), production costs for HR soybean were €25/hectare lower than those for non-GE varieties, but the authors noted that this result is not robust, being based on only six studies. Klümper and

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[9] The committee again emphasizes that the studies of the economic effects of *Bt* eggplant were anticipatory and, as was discussed in Chapter 3, *Bt* eggplant had not been approved for commercial release in India or the Philippines at the time the committee wrote its report.

Qaim (2014) looked at HR soybean, maize, and cotton together and found that profit increased by 64 percent for adopters of HR crops, largely because of increased yields (9 percent) and decreased herbicide costs (25 percent).

In the United States, Fernandez-Cornejo et al. (2014) summarized the findings of studies of net returns of HR soybean, HR maize, and HR cotton. Of eight studies published in 1998–2004, three reported that net returns for HR soybean adopters were the same as for farmers of non-GE soybean, and five reported an increase for adopters. Fernandez-Cornejo et al. were able to identify only three studies that produced information on net returns for adoption of HR maize and three for HR cotton. For HR maize, a 1998 study found net returns to be the same between adoption and non-adoption; in two 2002 studies, one reported a small increase in net returns to HR maize farmers, the other an increase. For HR cotton, a study from 1998 reported that net returns were the same; two studies from 2000 stated that net returns had increased for HR cotton farmers.

Gardner et al. (2009) focused specifically on labor savings in the United States from HR soybean, HR and *Bt*-HR maize, and HR and *Bt*-HR cotton. Their analysis showed that HR soybean saved household labor an average of 14.5 percent, enough to provide an incentive to use the technology. There was no evidence that HR maize offered household labor savings, and the evidence that *Bt*-HR maize saved household labor was extremely weak. The evidence in this study that HR or *Bt*-HR cotton provided labor savings was also weak. Fernandez-Cornejo et al. (2005) also provided strong evidence that herbicide resistance in soybean saved labor because it saved time spent on management. Their results showed that the adoption of HR soybean allowed labor to shift from farm management to off-farm employment, a shift that led to higher off-farm income. Their results did not show a correlation between the adoption of HR soybean and on-farm income. Results for HR soybean and labor allocation in the United States are qualitatively similar to those reported by Smale et al. (2012) for HR soybean in Bolivia, where HR soybean was identified as saving labor. A previous National Research Council report (NRC, 2010a) and Marra and Piggott (2006) also reported that nonmonetary considerations (such as savings in the time and effort spent on labor or management, savings on equipment, better operator and worker safety, improved environmental safety, and increased overall convenience) may be important in explaining HR crop adoption in the United States and in other countries.

Gonzales et al. (2009) summarized cost-efficiency and profit data reported on HR maize and *Bt*-HR maize in the Philippines in the wet and dry growing seasons of 2007–2008. Looking at the average yield, they found a small but constant advantage in cost efficiency for the HR varieties compared with conventionally bred hybrids in both seasons. The same was true of *Bt*-HR varieties. Afidchao et al. (2014) looked at economic results on HR maize and on HR maize that also contained at least one *Bt* trait in 2010. Fertilizer costs were higher for HR maize hectares than for non-GE maize hectares. The same was true when they compared *Bt*-HR maize with non-GE maize. Expenditures on herbicides and insecticides for both GE varieties did not differ from such expenditures for non-GE maize, and farmers did not report labor savings as a reason for adopting GE varieties. The net incomes of *Bt*-HR maize producers and HR maize producers were not statistically different from those of non-GE producers, and no profit advantage was found for either GE variety over non-GE maize. Further regression analysis led Afidchao et al. to conclude that even though *Bt*-HR maize had drawbacks with respect to seed and fertilizer costs, better control of insects and weeds probably provided adopters with an economic advantage.

In 2007, the first year of GE sugar beet production in the United States, Kniss (2010) compared 11 glyphosate-resistant sugar beet fields in commercial production with comparable non-GE sugar beet fields in Wyoming. Growers managed each pair of fields independently of outside advice. Growers paid a $131/hectare royalty for the HR sugar beet seeds. There was little difference in the number of herbicide applications between the two sets of fields, but herbicide costs were much lower for the fields on which glyphosate was applied because glyphosate was less expensive than the herbicides used on the non-GE sugar beet. On the HR sugar beet fields, growers spent less time tilling those fields, and no hand-weeding was done, whereas all non-GE fields were hand-weeded at an average cost of $235/hectare.[10] Root yield was 15 percent greater in the HR sugar beet fields, and their harvest costs were therefore greater than for non-GE sugar beet fields. Sugar content was similar in the two types of fields. Total sucrose content of the HR sugar beet fields exceeded that of the non-GE fields by 17 percent. Despite higher harvesting costs and the expense of the technology fee, Kniss found that the net economic return to growers of HR sugar beet was $576/hectare more than that of growers of non-GE sugar beet. The study could not be repeated in the following year to see whether results were similar because adoption of HR sugar beet had become so high that comparable non-GE fields could not be identified for study.

Income Effect of Early Adoption

Feder and O'Mara (1981) and Feder et al. (1982, 1985) described in detail issues experienced by farmers in developing countries who are

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[10] Kniss (2010) noted that the cost of hand-weeding was higher than other sugar beet growing areas because of a shortage of labor in Wyoming. He also stated that growers in other sugar beet growing areas of the United States often substituted herbicide applications for hand-weeding.

the first to adopt new technologies. Their focus was to identify the constraints on technology adoption and the potential income gains available to early adopters compared with late adopters. Their work was in line with previous research on new technologies in agriculture (Ryan and Gross, 1943). Early adopters of a technology gain economic benefits as their yields increase. However, as commodity prices drop because of increased production, later adopters may get yield increases but smaller economic benefits, so they earn less income than early adopters. Despite their late adoption, however, they are better off than those who chose not to adopt the technology; nonadopters earn even less income, and this can ultimately contribute to the loss of the farm. That phenomenon, termed the technology treadmill by Cochrane (1958), has been observed in the outcomes of the Green Revolution technologies in developing countries (Evenson and Gollin, 2003) and in the consolidation in ownership of U.S. farmland (Levins and Cochrane, 1996).

In the specific case of GE crops, Glover (2010) and Stone (2011) noted that the first farmers to use genetic-engineering technology in a new crop or a new location are not random; early adopters are more likely to be successful farmers. A similar observation was made by Smale and Falck-Zepeda (2012). The committee points out that many economic analyses examined in this chapter were carried out in the first decade of GE crops; the earlier gains found in those studies may taper off over time (see Box 6-1).

Synopsis

The available evidence from studies examined above indicates that the commercialization of HR soybean, *Bt* maize, *Bt* cotton, *Bt*-HR maize, and *Bt*-HR cotton has generally had favorable results in economic returns to producers who have adopted genetic-engineering technology, but there is high heterogeneity in outcomes. As has been pointed out in much of the same literature, the results are dated or not comprehensive. There have been few long-term, cross-sectional, or longitudinal studies. Studies have concentrated on one trait–crop combination (*Bt* cotton) in three countries (India, South Africa, and China). Furthermore, Smale et al. (2009) concluded from a review of many of the same studies covered in the meta-analyses discussed above that most of the studies have used a partial-equilibrium approach in which other sectors of the economy are assumed to be fixed and by design not allowed to adjust to changing economic conditions. That limitation may lead to an incomplete assessment because other approaches may allow for such adjustments. Studies of the first decade of GE crop adoption have faced substantial data limitations and methodological gaps that limited the robustness of their results, but methods have become more sophisticated and types of analyses have increased.

In general, studies of income effects have not looked as much at other widely grown crops with input traits such as HR canola and HR sugar beet or crops with resistance to viruses, including papaya and squash. Their high adoption rates where they have been approved and grown[11] imply that they provide an economic benefit to adopters. Studies conducted in Canada provide evidence on the economic benefits to adopters of HR canola (see Phillips, 2003; Beckie et al., 2006; Gusta et al., 2011; Smyth et al., 2014a). Studies of income effects after adoption of more recently commercialized crops, such as *Bt* eggplant or drought-tolerant maize, have yet to be done.

Although the existing economic-assessment literature points to overall gains to farmers of the most widely grown GE crops, there may be substantial variations in costs and benefits among producers, regions, and trait–crop combinations and over time. Pemsl et al. (2005), Raney (2006), Tripp (2009a,b), Glover (2010), Gouse (2012), and Fischer et al. (2015) noted that institutional issues influence whether farmers—especially small-scale, resource-poor farmers—are able to tap into the purported benefits of GE crops. In the next section, the intersection of the institutional variables is examined to determine the benefits of genetic engineering to small-scale and other farmers. Although the section focuses on small-scale farmers, the institutional issues are not exclusive to them.

FINDING: The available evidence indicates that GE soybean, cotton, and maize have generally had favorable outcomes in economic returns to producers who have adopted these crops, but there is high heterogeneity in outcomes. Earlier economic studies had data and methodological limitations, but there is progress in advancing methods and in the number of issues addressed in analyses beyond economics.

FINDING: In situations in which farmers have adopted GE crops, especially those with herbicide resistance, the committee finds that nonmonetary considerations are probably driving adoption of GE crops despite the absence of a readily identifiable economic benefit related to their production.

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[11] HR varieties were grown on 97.5 percent of canola hectares in Canada and 93 percent of canola hectares in the United States in 2012 (James, 2012). Adoption was lower in Australia, which approved HR canola for commercial production in 2008. In 2015, HR canola was planted on 30 percent, 13 percent, and 11 percent of canola hectares in the three Australian states that permit HR canola to be grown, for a total of 436,000 hectares (Monsanto, 2015). Ninety-seven percent of sugar beet planted in the United States in 2012 was herbicide resistant (James, 2012). USDA estimated that most of the 14,200 hectares of sugar beet planted in Canada in 2012 was herbicide resistant (Evans and Lupescu, 2012).

Benefits to Small-Scale Farmers

The question of the benefit of genetic engineering to farmers is tricky. Who is the farmer in question? Most studies of GE crops in developing countries have focused on the benefits of the technology at the farm level. Most confirm that farmers have benefited from adopting and using the technology on the basis of such metrics as gross income, extent of insecticide use, and yields. However, the question of benefits of genetic engineering by size of farmer land holding needs to be discussed in more detail. There are important differences among countries, crops, and type of production system. In addition, attention needs to be paid to the separation of benefits of crop improvement from conventional breeding and benefits of a GE trait.

This section discusses the utility of both the existing GE trait–crop combinations and the technology itself to small-scale farmers. The committee considered small-scale farmers as defined in the studies examined. Globally, small-scale farmers are considered to be those who manage 5 hectares or less, but this definition does not fit all small-scale farmers (Box 6-3; HLPE, 2013; MacDonald et al., 2013). The category of small-scale farmers includes those who are resource-poor—that is, they are constrained in terms of capital and labor.

Farm size is generally seen as a proxy for or indicator of economic resources available to farmers. The committee received many comments asserting that commercially available GE crops have benefited large-scale farmers more than small-scale farmers. Farm size is influenced by factors other than the type of crops grown (see discussion of "disappearing middle" in Box 6-3 and Tripp, 2009a), but it is still relevant for assessing the social and economic benefits of GE crops.

The committee concentrated its review on these smaller operators for a number of reasons. Large-scale farmers of crops with GE traits have adopted them widely in the countries where they are approved; that circumstance, combined with the economic benefits reviewed above, leads the committee to conclude that genetically engineered IR and HR crops have generally been useful to these farmers so far. Whether those crops and genetic engineering itself are relevant to small-scale farmers is less clear, in part because they are such a diverse group with different livelihood portfolios and competing goals, only one of which may be yield optimization (Soleri et al., 2008; Jayne et al., 2010; Giller et al., 2011).

Benefits of Existing Genetically Engineered Crops

The most widely grown GE crops—HR soybean, *Bt* maize, *Bt* cotton, *Bt*-HR maize, *Bt*-HR cotton, and HR canola—were first commercialized in the United States, where they were grown primarily on large-scale farms.

BOX 6-3
Farm Size and the "Disappearing Middle"

Farms may range from less than 1 hectare to more than 10,000 hectares (Lowder et al., 2014; van Vliet et al., 2015).[a] Depending on a farm's available economic resources and production goals, operations may be entirely manual or entirely mechanized. For similar reasons, a farm may use no labor other than that of the operator or could provide work for a large crew of temporary or full-time laborers. There is tremendous variety in what can be produced on a farm and on what scale. Thus, the term *farm* encompasses a wide array of agricultural production systems.

The Food and Agriculture Organization (FAO) estimates that there are at least 570 million farms in the world (Lowder et al., 2014),[b] most of which are smaller than 2 hectares (Figure 6-1). Given incomplete data, FAO estimated that the small farms operate about 12 percent of the world's farmland. As the income level of a country increases, average farm size increases as does the share of farmland controlled by larger farms (Lowder et al., 2014).

On a global scale, the agricultural labor force increased during 1980–2013, from 962 million to 1.3 billion (FAOSTAT, 2015). Although the number of people working in agriculture grew over that time, the percentage of people involved decreased. The percentage of the world's population economically active in agriculture decreased during 1980–2013 from 21.6 percent to 18.6 (FAOSTAT, 2015).

The area of land farmed has not increased nearly as much as the number of people involved in farming; from 1960 to 2000, average farm size declined, but the general trend masks the story told when income groups are examined separately. FAO data show that farm size in low-income, lower-middle-income, and upper-middle-income countries declined while farm size in high-income countries increased (Lowder et al., 2014). That phenomenon—the disappearing middle in size of farm operations—has been reported in Africa (Byerlee and Deininger, 2013), Europe (Mandryk et al., 2012; EUROSTAT, 2014), and the United States (MacDonald et al., 2013). On the one hand, economic pressure leads to consolidation of farms into larger units; on the other hand, farm division through inheritance leads to fragmentation into smaller units (van Vliet et al., 2015).

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[a] Family farms, in which the family is the main source of labor or the farm is passed from one generation to the next, predominate in all parts of the world and cannot be equated with smallholdings (van Vliet et al., 2015).

[b] The FAO definition of *farm* excludes forestry and fisheries. Because the collected data are not uniform, FAO used the agricultural unit reported in countries' agriculture censuses to estimate the number of farms worldwide (Lowder et al., 2014).

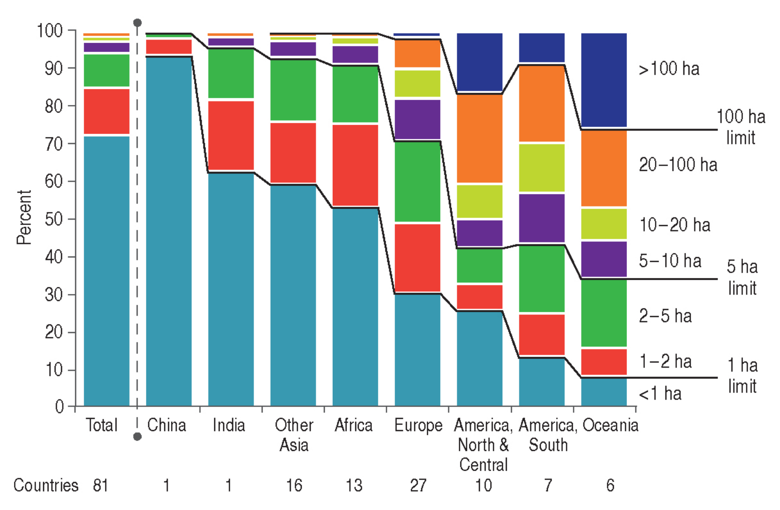

FIGURE 6-1 Diversity in farm size by region.
SOURCE: HLPE (2013).
NOTE: Figure is based on data from 81 countries.

However, some of these trait–crop combinations, particularly *Bt* cotton, have been adopted by small-scale farmers in different regions of the world. Most of the studies focused on developing countries—India, China, and Pakistan—that have large numbers of smallholder farmers show gains from the adoption and use of GE crops. In the case of cotton, a substantial body of evidence shows that countries that have become world leaders in cotton production (India, China, and Pakistan) use *Bt* cotton and that the use of those varieties has created benefits to smallholder farmers. However, there is also evidence that the benefits of these crops to small-scale farmers in other regions have been mixed.

Bt *Cotton.* Glover (2010) was doubtful of *Bt* cotton's benefits to small-scale farmers in less developed countries and equally critical of the narrative that he identified in the scientific literature and popular press that supported IR crops as a "pro-poor technology." Among his criticisms was that although *Bt* traits in cotton provided yield protection in seasons with heavy pressure from target insects, in seasons without high infestations adopters of *Bt* cotton have paid more for the GE trait or traits but have not received any economic benefits. *Bt* traits also did not protect cotton growers from potentially increased populations of secondary insect pests, whose control could be expensive in insecticide expenditures, labor costs, or time required. Those circumstances would be true for all adopters of *Bt* cotton, but Glover's point was that small-scale farmers are in a more financially precarious position than large-scale farmers; if economic benefits do not materialize, small-scale farmers are more adversely affected by their lack of return on the investment in the *Bt* trait.

In their comparison of 36 farmers who grew either *Bt* cotton *Gossypium hirsutum* L. or non-*Bt* cotton *G. arboreum* under rain-fed conditions in Maharashtra, India, Romeu-Dalmau et al. (2015) found that there was a positive correlation between how much farmers of *G. arboreum* spent on inputs, such as insecticides, and how much revenue they received. In contrast, there was no correlation between how much farmers of *Bt G. hirsutum* spent on inputs and how much net revenue they received; this suggested to the authors that adopters of *Bt* varieties, many of whom are small-scale farmers, did not have adequate skills to optimize their return on investment with *Bt G. hirsutum*. Glover (2010) pointed out that insecticide overapplication on *Bt* cotton fields was also observed by Qaim (2003) in India and Pemsl et al. (2005) in China. Qaim and Pemsl et al. attributed insecticide overapplication to poor dissemination of knowledge about using the technology; overapplication tended to decrease or disappear when farmers learned more about the technology.

Earlier studies of the economic returns to small-scale farmers from the adoption of *Bt* cotton in the Makhathini Flats of South Africa found gains from the adoption and use of the technology (Gouse et al., 2005; Gouse, 2009). However, follow-up studies in the region—some conducted by the same authors as the original studies—have documented the poor long-term durability of the gains. Those studies pointed out the need for examining institutional issues related to the use of such technologies, especially in developing countries. One study found that, despite labor savings, *Bt* cotton varieties in smallholder farming systems that were not operated intensively did not make economic sense because of the high price of seed and the continued need to spray chemicals for pests not affected by *Bt* (Hofs et al., 2006). The Hofs et al. study benefited from multidisciplinary collaboration, use of isogenic lines as counterfactual comparator, and detailed daily data, but it used a small number of farmers (20 in total) in close proximity to one another (Smale et al., 2009).

Initial adoption of *Bt* cotton was strong among smallholders in the Makhathini Flats in 1997–2001, rising to nearly 3,000 farmers (90-percent adoption rate) in 2001 (Gouse, 2012). However, once extension services and available credit from a private cotton-ginning company that monopolized the buyer's market ended in 2001, the number of smallholders who continued to use *Bt* cotton declined dramatically (Gouse, 2009, 2012; Schnurr, 2012). Fok et al. (2007) reaffirmed the conclusion reached by multiple earlier studies that smallholder adopters of *Bt* cotton in the Makhathini Flats accrued economic benefits in a time period characterized by high target-insect pest pressure. The authors raised a cautionary tale about focusing only on the economic benefits without discussing the particular institutional context in which the cotton was deployed.

The institutional context becomes apparent when later *Bt* cotton production in the region was encouraged by another monopoly that became the region's sole cotton buyer in 2002. It supplied *Bt* seed but favored large-scale operations or entered into joint ventures with smallholders to operate their land as larger units. The number of independent smallholder farmers cultivating cotton (*Bt* or non-*Bt*) in the Makhathini Flats fell from 2,260 in 2007–2008 to 210 in 2009–2010 (Gouse, 2009, 2012). Schnurr (2012) reported that average yield in 2009–2011 for smallholders was 8 percent greater than it was in 1996–1998 (before *Bt* cotton was introduced), much different from the 40-percent increase reported after the initial adoption period around 2001. In general, cotton production—GE or otherwise—has declined in South Africa for large and small farmers since the 2003–2004 season because of a downturn in the price of cotton compared with the prices of maize, soybean, and sunflower (*Helianthus annuus*) (Gouse, 2012).

Dowd-Uribe (2014) observed a similar connection between reliable credit and *Bt* cotton production in Burkina Faso. An entity controlled partly by the government that supplied credit allowed Burkinabè cotton farmers to purchase seed, fertilizers, and insecticides; it also provided a guaranteed market for the cotton, putting farmers in a more secure position to pay the premium for *Bt* cottonseed. The state's pricing structure contributed to the crop's adoption after its market introduction in 2008. Burkinabè cotton farmers paid for *Bt* cottonseed by the hectare rather than by the seed stack, so they were able to adjust planting density to local conditions, including rainfall variability, without a price penalty. Those institutional supports could create longevity for the adoption of *Bt* cotton in Burkina Faso, the only African country with GE crop production in which smallholders farm most of the agricultural land. However, Dowd-Uribe (2015) expressed doubt about the value of GE cotton to resource-poor smallholders in Burkina Faso on the basis of his observations about the price of seed, the lack of refugia (which is likely to lead to insect resistance), and government corruption. That skepticism has received some confirmation: Burkina Faso has since begun phasing out GE cotton (Dowd-Uribe and Schnurr, 2016). One of the suggested reasons for the phase out is that the particular GE variety was deemed inferior to other non-GE varieties. However, the authors also documented various institutional challenges—such as loss of credit access, market disruptions, the failure to cross the *Bt* trait into local varieties, and the high cost of seed in South Africa and Burkina Faso—as related to declining interest in GE cotton (Dowd-Uribe and Schnurr, 2016). Vitale et al. (2008, 2010) found that economic gains from *Bt* cotton adoption among Burkina Faso farmers were subject to how the value-chain structure is organized in Burkina Faso and to changing economic conditions related to the international cotton market, in which low-cost producers—such as India, China, and Pakistan—dominate different segments of the market.

Bt *and HR Maize.* With regards to maize, Gouse (2012) noted that, although GE maize varieties had been widely adopted in South Africa by large-scale farmers, adoption by smallholders had been minimal because of the difficulty of getting seed to them. In the Hlabisa municipality, where he conducted household surveys over eight seasons, he observed that farming was not the main income of smallholders, and this was also the case for most South African smallholders.[12] He examined the effects of the adoption of GE white maize by households in this community, where white maize is a subsistence crop. A *Bt* variety of white maize was first commercialized in 2001, and this was followed by an HR variety in 2003 and a *Bt*-HR variety in 2007. Gouse compared non-GE, *Bt*, HR, and *Bt*-HR varieties in

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[12] Surveyed households in Hlabisa received most of their income from pensions, government grants for children, remittances, and off-farm income.

the seasons of 2005–2006, 2006–2007, 2007–2008, and 2009–2010[13] and found that *Bt*-HR maize had greater yields that were statistically significant in each year in which it was grown. However, when it came to net farm income, the HR variety was the top performer over non-GE, *Bt*, and *Bt*-HR varieties in three of the four seasons, even though the *Bt* variety had greater yields in most seasons. The HR variety's advantage was partly because of greater yields but mostly because of the time savings on family labor. Surveyed farmers told interviewers that they were interested in having the HR trait incorporated into the older, less expensive, more drought-tolerant popular maize hybrid (PAN 6043) commonly grown in the region.

In an earlier study of the Hlabisa municipality, Gouse et al. (2006) found that *Bt* maize grown by smallholders over three seasons was economically more profitable than non-GE hybrids but only in years and locations where there was substantial insect-pest infestation. Farmers have no way of predicting pest levels before investing in the higher seed costs—a problem similar to that stated in Glover's (2010) critique of *Bt* cotton production on small farms. However, the findings of Klümper and Qaim (2014) qualify that critique with the argument that for smallholders in developing countries, despite higher prices for GE seed, the costs of inputs (chemical and mechanical pest controls) decline; this partially explains why *Bt* varieties were more profitable for smallholder farmers in developing countries. This outcome then connects *Bt* varieties with the access to credit.

Mutuc et al. (2013) used a dataset consisting of 470 farmers (107 *Bt* and 363 non-*Bt* maize farmers) from Isabela Province in Northern Luzon in the Philippines for crop year 2003–2004. The authors found—after taking into consideration and correcting for the effects of statistical biases and for the fact that some data for insecticide use are only partially known—a small but statistically significant effect of *Bt* maize adoption on yields and profits and reductions in the likelihood of insecticide use and demand. The authors also showed an influence of *Bt* maize adoption in reducing fertilizer use. Their study obtained qualitative results similar to those of an earlier study by Mutuc et al. (2011) that used a different estimation method. Also in the Philippines, Yorobe and Smale (2012) reported results of a study of 466 maize farmers in 17 villages in Northern Isabela in Luzon and South Cotabato in Mindanao in 2007–2008. The total sample consisted of 254 *Bt* and 212 non-GE hybrid users. The authors corrected for selection bias by using statistical estimation methods for biases and the effects of unobserved variables. The study showed that adoption of *Bt* maize increased yields and net farm, off-farm, and household income compared with non-GE hybrids

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[13] In 2005–2006 and 2006–2007, non-GE, *Bt*, and HR varieties were compared. In 2007–2008, all four varieties were compared. In 2009–2010, non-GE, HR, and *Bt*-HR varieties were compared.

used in the Philippines. It is important to note that these studies tend to show that adopting farmers in the Philippines are better off—that is, have higher income, more education, and a favorable view of technology in general—than nonadopting farmers.

In contrast, Afidchao et al. (2014) reported that small-scale, including resource-poor, farmers in the Philippines adopted GE maize after large-scale farmers. The authors used purposive sampling, which implies that it is not statistically representative of the population and may lead to questions about the generalizability of the results. Farmers seem to have adopted GE maize because they were curious and because they expected better yields and insect control and reduced input costs. However, Afidchao and colleagues conducted a survey and found that some small-scale farmers who had adopted *Bt* maize did not think their economic status had improved after adoption of the technology. About 25 percent of survey respondents who adopted maize with *Bt* and HR traits said that they no longer agreed with the statements that GE maize is worth investing in and could improve farmer livelihoods. In a 2014 study, Afidchao and colleagues assessed the economic effect of *Bt*, HR, and *Bt*-HR varieties of maize on Filipino small-scale farmers in one province;[14] the results are described in the section above on income effects. With respect to benefits, the authors concluded that farmers with more economic capability were more likely to avail themselves of the advantages that GE crops offer. Farmers who could not afford herbicides were likely to continue manual weeding even when HR or *Bt*-HR varieties of maize were planted. Other farmers continued to use insecticides to control insect pests not targeted by *Bt*. Afidchao et al. noted that the high costs of GE seeds in combination with high interest rates associated with credit decreased the potential economic advantages of GE maize varieties. They concluded that the social and economic conditions observed with respect to seed costs and lending costs and the inability to exploit the technology's potential could keep GE maize varieties from being economically advantageous compared with non-GE varieties for resource-poor farmers in the Philippines. That outcome could explain the results of their survey, which found that many adopters did not think GE varieties had been worth the investment.

HR Soybean. As mentioned above in the discussion of income effects, HR soybean has been studied far less than other GE varieties. HR soybean is the most widely grown GE trait–crop combination in medium-income and high-income countries; most of the hectares planted are produced on large farms in the United States, Brazil, and Argentina. One study of smallholders producing HR soybean in Bolivia was identified, with the caveat that small-

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[14] Ninety percent of farmers surveyed by Afidchao et al. (2014) had farms smaller than 3 hectares; 10 percent qualified as large-scale farmers, with farms of 4–8 hectares.

scale soybean farmers surveyed in 2007–2008 by Smale et al. (2012) were considered to be those who planted less than 50 hectares. Those farmers made up 77 percent of soybean producers in Bolivia; large-scale operators managed farms of more than 1,000 hectares and made up only 2 percent of farmers. It is of note that even small-scale Bolivian soybean producers had access to farm machinery. Smale et al. (2012) found that HR soybean growers in Bolivia were likely to operate more farmland, have more education, and own more farm machinery than nonadopters and were more likely to own their farms. A problem reported by the authors was finding the small-scale nonadopters, who had different characteristics from adopters and were more likely to take advantage of a government program that would subsidize their production if they planted non-GE soybean. Nearly all HR soybean growers said that management of targeted weeds was easier than with non-HR soybean. Their yields were greater than those on non-HR soybean farms, and 76 percent reported that HR soybean production required less time devoted to labor by members of the family who were not the primary farm operator. That reduction allowed family members more time to earn off-farm income, which contributed to the higher total household income of adopters than of nonadopters.

Høiby and Zenteno Hopp (2014) reported that by 2013 almost all the soybean crop in Bolivia, regardless of farm size, was planted with HR soybean. They noted criticism has been made that small-scale farmers had no options other than HR soybean because of private-sector control of the seed and credit markets. It is not clear whether farmers wanted non-GE soybean varieties and did not get access to them or whether non-GE varieties are not available because there is no demand for them. Those questions need further research. However, Høiby and Zenteno Hopp also recounted that government efforts to support non-HR soybean production were unsuccessful because credit and seed were not delivered to farmers in a timely manner, whereas private-sector companies supplied GE seed, credit, and technical support to farmers punctually.

Bt *Eggplant.* *Bt* eggplant had not been commercialized long enough or widely enough for the committee to assess whether smallholders will find this product useful. However, it is a GE crop that could provide benefits to smallholders. In India and Bangladesh alone at least 1.5 million smallholders grow eggplant (Kumar et al., 2010; Choudhary et al., 2014), and eggplant is an important crop throughout Asia. Eggplant fruit and shoot borer is frequently cited as one of the most destructive pests in the region (Islam and Norton; 2007; Krishna and Qaim, 2008). Ex ante assessments of the economic and health effects of *Bt* eggplant have reported numerous benefits to farmers' bottom lines through costs savings and to their health through reduced insecticide use (Islam and Norton, 2007; Krishna and Qaim, 2008; Kumar et al., 2010; Francisco et al., 2012; Gerpacio and Aquino, 2014). However, those projections were called into question in Andow's critique of the Indian government's environmental risk assessment of *Bt* eggplant. Andow (2010) noted that the *Bt* eggplant variety evaluated by India's regulatory authority was a hybrid and therefore unlikely to be useful to smallholders who grow one or more open-pollinated varieties (OPVs). He concluded that adoption of a hybrid variety, which could not be self-propagated, would adversely affect smallholders' economic security. He declined to comment on the utility of OPVs with the *Bt* trait—which private-sector developers had plans to make available to farmers at a minimal cost—because the varieties had not yet been brought forward for regulatory approval. Andow also posited that the *Bt* trait would be less useful to smallholders than to large-scale growers because smallholders have more options to use damaged fruit than do large-scale growers. He suggested that increased income from *Bt* eggplant would be only 8,025 rupees/hectare for smallholders if they even adopted the hybrid and that integrated pest management (IPM) with non-*Bt* varieties could make the same inroads in combating eggplant fruit and shoot borer, reducing insecticide use, and increasing income for smallholders (by 164,923 rupees/hectare in his estimate) with more certainty than would adoption of *Bt* eggplant.

Andow's review was conducted when only hybrid *Bt* eggplant was available. That is no longer the case (Kolady and Lesser, 2012). A two-track approach was planned for the release of the technology, in which the private company MAHYCO would pursue hybrid *Bt* eggplant and two agricultural universities would pursue the development of OPVs of *Bt* eggplant. The distinction that Andow made between the hybrids and the OPVs for regulatory purposes would therefore cease to be an issue. Regulatory approval for the trait in India is currently limited to a specific host variety; use of the genetic construct in other varieties requires an expedited permit. That used to be an issue when approval in the Indian system had to be for the event-variety combination, but this is not the case anymore.

The comparison of *Bt* eggplant with non-GE eggplant with IPM may be partially incorrect if estimates Andow presented were for net returns from IPM, which may be for complete adoption of the IPM practices. In most cases, IPM adoption is incomplete and net return may be much smaller. If Andow chose to have a relative number to separate adoption from partial adoption (say adopt 5 of the 10 practices in the IPM package to be considered an adopter) and the net return reflected that, this may not be an overestimation. Furthermore, Andow (2010) cited incorrectly Krishna and Qaim (2008), who compared *Bt* eggplant with non-GE eggplant, and stated that these authors base their estimates solely on experimental trials. In fact, Krishna and Qaim also conducted a survey of 360 eggplant farmers in three states to calculate farm-enterprise budgets.

Krishna and Qaim discussed pricing and the effect of the strategy of pursuing hybrids and OPVs for *Bt* eggplant in India. This is an important discussion in that it affects other public-private partnerships that seek deployment of GE crops to farmers in developing and even developed countries. In their view, selling *Bt* eggplant OPVs at a much lower price than *Bt* eggplant hybrids may increase social welfare inasmuch as some resource-poor farmers, who previously were income-constrained or lacked access to credit, may be able to tap into the technology. However, some farmers who were planting eggplant hybrids may opt for the OPV *Bt* eggplant because it may have a lower cost. The latter would affect the revenue stream for the private-sector developers.

Kolady and Lesser (2006) reported on the results of a survey of 290 farmers in Maharashtra, India, conducted in 2004–2005. Survey participants included eggplant and non-eggplant vegetable farmers who grew cultivated hybrid and OPVs. Results of the estimated adoption statistical model show that farmers using hybrids were likely to adopt a *Bt* hybrid eggplant whereas OPV eggplant farmers were likely to adopt a *Bt* OPV. The proposed public–private partnerships that would develop *Bt* hybrids and OPVs for different farmer target groups had a reasonable chance of being successful. Farmers who have shown a preference for greater yields (hybrid-eggplant farmers) were likely to adopt *Bt* hybrids even if *Bt* OPVs were available at a lower price than the *Bt* hybrids.

The ex ante studies reviewed above suggest there are economic opportunities for small-scale eggplant farmers associated with adoption of *Bt* hybrids or OPVs, but at the time the committee was writing its report, only a small number of farmers in Bangladesh were using *Bt* eggplant varieties. The experience of smallholder *Bt* eggplant farmers remains to be seen.

Virus-Resistant Papaya. Genetically engineered virus-resistant (VR) papaya was adopted rapidly in the U.S. state of Hawaii when it was commercialized in 1998. Papaya production in the state had fallen by more than 30 percent from 1992 to 1997 because of the damage to fruits and ultimately the death of papaya trees due to papaya ringspot virus (VIB, 2014). Hawaiian small-scale growers (0.4–2.4 hectares) were the quickest to adopt the variety when it became available in the late 1990s because they were losing more area to the virus than were larger growers (Gonsalves et al., 2007). In 2000, adoption of the VR variety was 42 percent; it had grown to 77 percent by 2009 (USDA–NASS, 2009). The number of hectares planted with papaya held steady over that time. Scientists in China developed a VR papaya that targeted local strains of the ringspot virus in 2007. By 2012, more than 60 percent of papaya hectares in China produced VR varieties (VIB, 2014).

Unlike HR crops, VR papaya is not associated with labor savings, and insecticides need to be sprayed on VR papaya the same as for non-GE papaya. However, there are no additional inputs or capital investments needed to grow the GE variety; it is wholly substitutable for its non-GE counterpart (Gonsalves et al., 2007). Also, no economies of scale are peculiar to VR papaya relative to non-VR papaya, according to Gonsalves et al. (2007), the developers of the VR papaya. Intellectual-property issues were negotiated for the Hawaiian-grown crop between public universities and the private sector, and the seeds were initially provided to growers at no cost.

The United States is a small producer of papaya on the global stage. In 2013, India was the world's largest producer, followed by Brazil, Indonesia, Nigeria, and Mexico (FAOSTAT, 2015). Commercial-scale production takes place in those countries and elsewhere, but in many developing countries papaya is often grown on a small scale or even in people's yards as a subsistence crop. VR papaya varieties to combat local papaya ringspot virus strains have been developed and field-tested but not commercialized in Brazil, Taiwan, Indonesia, Malaysia, Australia, Jamaica, Thailand, Venezuela, and the Philippines (Gonsalves et al., 2007; Davidson, 2008; VIB, 2014). The reasons for the lack of commercialization include organized opposition by nongovernmental organizations, the absence of a biosafety regulatory framework, and consumer wariness of VR papaya (Davidson, 2008; Fermin and Tennant, 2011). Therefore, although VR papaya appears to have many qualities that are conducive to production by small-scale farmers, its utility cannot be rigorously evaluated because it has been adopted in only two countries. The growth in adoption rates in the United States and China can be interpreted as preliminary evidence that papaya growers find the VR trait useful.

Apart from the benefits of any specific trait-crop combination, the amount of control that smallholders perceive to have over their own production practices and decisions may be an issue of concern related to existing GE crops. In one study in Brazil, smallholders interviewed felt that an adverse consequence of GE crops was the loss of control over their production practices and decisions (Almedia et al., 2015). The farmers indicated their perception that companies' control of the production of GE seeds may threaten their independence. Similarly, Macnaghten and Carro-Ripalda (2015) provided evidence that farmers in Mexico, India, and Brazil lack trust in the organizations and institutions responsible for delivering GE seeds and a concern about the loss of indigenous seeds. A study of Argentine smallholders found that many perceived that GE crops contributed to detrimental social changes, specifically, renting of their land for commercial production of HR soybean, which led to the loss of skills and identity as farmers and to rural emigration (Massarani et al., 2013). Tripp (2009a:20) argued that "farmers' control over a technology is determined by the quality of information available regarding its characteristics, information about relevant alternatives, and opportunities to test and adapt the technology to local conditions. Neither states nor markets have been particularly successful at supporting opportunities for farmers to master new technology." It is important to note that farmers' perceptions of a loss of power and control are not limited to smallholders or to the adoption of GE crops. A number of farmers in many parts of the world, including the United States, have expressed a loss of autonomy, often linked to declining profitability and the changing structure of agriculture beyond the introduction of GE crops (Key and MacDonald, 2006; Pechlaner, 2010).

Prospects and Limitations for Genetically Engineered Crops in Development for Small-Scale Farmers

At the time that the committee's report was written, only a few GE traits had been incorporated into crops, and *Bt* eggplant, the only GE crop that had been specifically developed to address the needs of small-scale, resource-poor farmers, was planted by fewer than 150 farmers worldwide. However, many such traits that were designed with small-scale producers or poor consumers in mind were in development in 2015.

As discussed in Chapter 5, Golden Rice has been designed to have beneficial health outcomes for consumers in developing countries. In its information-gathering phase, the committee heard about additional genetic-engineering efforts under way on (McMurdy, 2015; Schnurr, 2015):

- Disease-resistant cassava in Nigeria, Uganda, and Kenya.
- Drought-tolerant maize in Tanzania and Uganda.
- Insect-resistant cowpea in Nigeria, Burkina Faso, and Ghana.
- Banana biofortified with vitamin A in Uganda.
- Disease-, insect-, and nematode-resistant banana in Uganda.
- Virus-resistant potato in South Africa, Indonesia, and India.
- Nutritionally enhanced sorghum in Kenya and South Africa.
- Virus-resistant sweet potato in Kenya and South Africa.
- Climate-resilient rice in Nigeria, Ghana, Uganda, India, and Bangladesh.
- Climate-resilient wheat and millet in India.

These efforts are being supported by a number of private–public partnership models (McMurdy, 2015). Schnurr (2015) posited that many of the GE crops, if commercialized, may be available to farmers with no technology fee for the GE traits. However, the only concrete examples that the committee had of how the technologies may be offered free as an intended policy are the Golden Rice project and Water Efficient Maize for Africa.

Some authors have argued that for the amount of investment in genetic-engineering approaches, solutions could have been found through non-GE means (Cotter, 2014; Gurian-Sherman, 2014) and greater investments in agroecological improvements. Furthermore in some situations, other investments may have higher priority. For example, Tittonell and Giller (2013) argued that small-scale farmers in Africa cannot take advantage of improved plant genetics until soil fertility and nutrient availability are addressed. However, many traits being developed with genetic engineering are not attainable with conventional breeding or agroecological approaches. For example, there is no resistance to maruca pod borer (*Maruca vitrata*) in sexually compatible relatives of cowpea (*Vigna unguiculata*) and no agroecological strategies that control the insect pest.

The argument that non-GE approaches cost less needs to be qualified in the context of regulatory systems and of the development of the systems around the world. Several active stakeholder groups have pushed for more and more complex regulations, inclusion of broader social and economic considerations, and other policy developments, which probably have introduced additional regulatory barriers and may have increased time to and cost of deployment or reduced the technologies delivered to farmers (Paarlberg and Pray, 2007; Paarlberg, 2008; Smyth et al., 2014b). Such policy outcomes were unquestionably influenced by political efforts by groups both for and against stricter regulation of GE crops (Scoones and Glover, 2009; Schnurr, 2013).

Some authors have indicated that the focus of commercialized traits on closing the gap between actual yield and potential yield and on the linkage of trait performance with such inputs as herbicides and insecticides ignores the priorities of some small-scale farmers (Hendrickson, 2015). The committee has documented benefits of GE crops to small-scale farmers in this chapter and in Chapter 4, but it recognizes that the traits, and sometimes the varieties in which a GE trait is available, are not appropriate for some small-scale farmers. For example, in maize and sometimes in cotton, most GE traits have been bred into hybrid varieties, but hybrids—genetically engineered or not—may not be the best or most desired option for all farmers with respect to economic returns. When a truly appropriate hybrid is available, it will generally outperform the best OPV under any conditions (including marginal production conditions without other inputs), but such hybrids often are not available. Langyintuo and Setimela (2007) found that to be the case with maize in Zimbabwe. Although it might be most appropriate for countries to develop hybrids that fit into subsistence agricultural systems, such investments are rare. Furthermore, a resource-poor farmer's investment in hybrid seed may be unacceptably risky unless the farmer has a reasonable probability of achieving or exceeding a minimum yield that depends on the market price of the crop (Pixley, 2006). Production of OPV seed is generally simpler and less expensive than production of hybrid seed, and farmers who grow OPVs can save their own seed for planting in the next season with often negligible loss of yield. Finally, many smallholder farmers grow crops for self-consumption rather than for the market, and their choice of variety to plant may be based on preferences and traditions quite removed from market considerations; an example is the South African maize farmers who would have preferred an HR trait in an older, locally grown, drought-tolerant variety (Gouse, 2012).

The committee heard from a number of presenters who stressed that for genetic-engineering technology to contribute to resolving issues of small-scale farmers, particularly those who are resource-poor, concurrent investments are needed in soil fertility, integrated pest management, optimized plant density, credit availability, market development, storage, and extension services (Hendrickson, 2015; Horsch, 2015; McMurdy, 2015; Schnurr, 2015). Furthermore, the committee recognizes that criticism of the level of investment in research and development (R&D) for GE crops would be especially relevant if a disproportionate amount of investment was directed exclusively to GE crops. That does not seem to be the case, as documented for Latin America (Falck-Zepeda et al., 2009) and Africa (Chambers et al., 2014). Hence, a diversified portfolio of R&D activities and investment in resolving production and institutional issues needs to focus on small-scale farmers. That approach needs to consider the overall investment strategies in developing innovative capacity in a country (Box 6-4).

Synopsis

There is a growing body of evidence that GE crop adoption has benefited many farmers in developed and developing countries. It is noteworthy, however, that several studies report mixed results regarding the benefits of commercialized GE crops for small-scale farmers. The higher price of GE seed and access to credit may have been important barriers—among other institutional issues—for some of these farmers to adopt the GE crops that have been commercially available since the 1990s. Although the GE varieties often produce greater yields and sometimes reduce other input costs, the committee examined a few case studies in which it was not always economically feasible for small-scale farmers to adopt GE crops or to continue planting in seasons after initial adoption. Those outcomes may be a result of GE crop varieties' being more expensive than alternatives and that available traits require additional inputs such as herbicides or insecticides. When credit has been provided, small-scale farmers have tended to adopt the crops and have had some success, but adoption declines when credit options disappear. Given those challenges, it is often the more economically prosperous small-scale farmers who plant GE varieties.

BOX 6-4
Investment Policies to Develop Capacity for Biotechnology Innovation

An investment policy designed to improve agricultural biotechnology and GE crops in a specific country needs to consider many alternatives. OECD (2003), Falck-Zepeda et al. (2009), and Chambers et al. (2014) described a conceptual framework in which two considerations guide the selection of policy instruments. The first is the science and technology capacity of a specific country. It implies an examination of the stock and flows of institutional, human, and financial resources invested in biotechnology research and development (R&D) in the country and the links between different components of the country's biotechnology innovation system. The second consideration is market size and the opportunities for biotechnology products to be developed by the innovation system.

Science and technology capacity and market size allow classification of countries into categories of innovative research capacity. Countries in a lower innovative capacity category that wish to improve their innovative capacity may need first to develop or improve basic R&D and technology-transfer capacities, such as plant breeding and basic molecular-biology applications. Alternatively, if a country desires to access innovations developed in other countries, it may need to ensure that it has a policy and regulatory environment that permits such transfer. Depending on existing capacity, it may be better for a country to pursue R&D in more basic agricultural technologies or conventional crop-improvement approaches instead of genetic-engineering technologies because these types of investment would increase its ability to improve its agricultural systems and its ability to tap into other countries' genetic technologies. The deciding factor should be society's returns on R&D investments.

There is evidence that HR maize in South Africa and HR soybean in Bolivia have been useful to smaller producers because the decrease in the time needed to plant seeds and weed fields has freed up family labor to pursue off-farm income. However, a small number of studies and reports have suggested that some small-scale farmers in Brazil have also reported a loss of autonomy because of reduction in seed choices and because of farm consolidation since the introduction of GE crops.

In some locations where GE crops were adopted and used, they did not prove economically advantageous to small-scale farmers in part because of credit constraints and the money and time spent on redundant insecticide applications. Those outcomes indicate an initial lack of familiarity with genetic-engineering technology and the need for extension services for small-scale farmers, especially in initial deployment. The committee heard from several presenters that such services were necessary whether or not GE crops are adopted. It also heard that small-scale farmers need assistance with many other agricultural practices—such as improving soil fertility, increasing nutrient availability, and optimizing plant density—with or without the introduction of GE crops.

The benefits to small-scale farmers of the GE crops that were commercially available to them in 2015 depended on the crop and the agricultural situation. In many cases, such conditions as available credit, affordable inputs, and extension services appeared necessary for those farmers to find genetic-engineering technology advantageous. From the information presented to the committee and other available information, it seems likely that a number of GE crops developed with small-scale farmer needs in mind may be commercialized as early as 2017. Unlike the first generations of HR and IR maize, soybean, and cotton released earlier to farmers, the crops listed above were being developed in collaboration with research institutions in countries for which they are designated (Chambers et al., 2014; Horsch, 2015; Schnurr, 2015).

> **FINDING: GE maize, cotton, and soybean have provided economic benefits to some small-scale adopters of these crops in the early years of adoption. However, sustained gains will typically—but not necessarily—be expected in those situations in which farmers also had institutional support, such as access to credit, affordable inputs, extension services, and markets. Institutional factors potentially curtail economic benefits to small-scale farmers.**
>
> **FINDING: VR 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 pesticides. Other technologies currently in the R&D pipeline—such as insect, virus, and fungus resistance and drought tolerance—are potential candidates to accomplish the same outcome especially if deployed in crops of interest to developing countries.**
>
> **RECOMMENDATION: Investments in GE crop R&D may be just one potential strategy to solve 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.**

Aspects of Farmer Knowledge

The subject of farmers' knowledge, practices, and customs appears commonly in agricultural research (Millar and Curtis, 1997; Bentley and Thiele, 1999; Grossman, 2003; Ingram, 2008; Oliver et al., 2012) but generally is not specific to GE crops.[15] There are many reasons that farmer knowledge, practices, and customs are of interest when focusing on GE crops. As one of the invited speakers remarked to the committee, "knowledge of actual farmer practice, and the farming systems in which it is embedded, is crucial to understanding the positive and negative impacts of any technology" (Hendrickson, 2015). Thus, the committee sought to examine the literature that it could find on different aspects of farmer knowledge as it pertained to GE crops, including the potential contribution of farmer knowledge in policy and regulatory formation, farmer-adaptive approaches to solving production constraints that GE crops also seek to address, and farmer skillsets as it relates to GE crops.

With regards to farmers' ability to contribute to regulatory structures, Mauro and McLachlan (2008) found that Canadian farmers of HR canola identified management benefits of GE crops, such as easier weed control, but they also noted a wide array of risks, including technology-use agreements and increased seed costs. Furthermore, perceptions of risks associated with HR canola tended to increase among farmers of smaller farms. The authors concluded that farmers' understanding of the performance of GE crops, such as volunteer weeds, could help to inform regulators but that regulators had ignored this type of practical knowledge.

Focusing specifically on how regulatory regimes respond to the potential contamination of food through the open-air production of biopharm plants, Goven and Morris (2012) argued that regulatory regimes of the United States, the European Union (EU), Canada, and New Zealand tend to exclude, even if unintentionally, farmer knowledge related to establishing regulatory policies. Their study focused on how seed farmers' experiential knowledge of managing seed-crop purity might inform biopharming regulation, which they argued is difficult to incorporate into existing risk-assessment and risk-management regulatory regimes. Although Mauro and McLachlan (2008) reported that regulators ignore farmers' knowledge because of the view that it is subjective and unreliable, Goven and Morris (2012) concluded that the lack of use of farmer knowledge is endemic in the operation of the regulatory system.

With respect to farmers' adaptive skills, McMichael (2009) was critical of private-sector efforts to patent "climate-ready" genes to develop

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[15] The discussion in this section is about knowledge practices at the farm level as opposed to debates surrounding the patenting of indigenous plants, or properties of the plant, by corporations.

drought-tolerant varieties of maize when farming women in West Africa were already managing recurring drought by selecting seeds conducive to the challenging conditions. Settle et al. (2014) showed that cotton farmers in Mali can adopt IPM systems through community-based educational programs that can markedly lower their use of and expenditures on insecticides without adversely affecting yields and without investments in new technology. However, beyond small scale or temporary successes, adoption of IPM by small scale farmers is very low (World Bank, 2005; Morse, 2009; Parsa et al., 2014) even though the IPM paradigm has been promoted since the 1960s. Widespread implementation will require careful investment and confrontation of practical problems (Parsa et al., 2014).

Some researchers have suggested that GE crops are actually contributing to a loss of skills among farmers. The concept of "deskilling" in agriculture emerged in the 1990s (Fitzgerald, 1993) and has been used intermittently to describe the consequences of technology for producers. The deskilling process has been defined as the "appropriation of labor whereby industry effectively eliminates skilled workers by introducing new technologies that defray labor costs and increase profits" (Bell et al., 2015:8). One of the first studies to apply the concept to agriculture had to do with hybrid maize. Fitzgerald (1993) argued that hybrid maize meant that farmers no longer relied on their own knowledge for seed selection, which often came through years of experimentation and conversations among farmers. Stone (2007) and Stone et al. (2014) made a similar claim with respect to *Bt* cotton producers in one district of India. They noted that agricultural deskilling preceded the arrival of *Bt* cotton in the district, with fads for some seeds being observed. In their analysis of 11 years of seed choices by farmers in the district, they found that the proliferation of *Bt* cotton seeds available to farmers created an environment that was inconsistent (because insect-pest population size could not be correlated with *Bt* efficacy), unrecognizable (because of the number of varieties available), and plagued by accelerated technological change (*Bt* cotton had first reached the district in 2005; by 2009, six *Bt* events were incorporated into 522 different hybrids). The confusion inherent in such an environment was, the authors concluded, consistent with exacerbation of agricultural deskilling (Stone et al., 2014).

Stone (2007) has acknowledged problems with using the concept of deskilling. Most notably, he stated that the concept implies the existence of an unrealistic, even romanticized, indigenous farmer skillset (see also Tripp, 2009a). However, employed carefully, the concept can highlight how a new technology can interrupt farmers' learning processes in relation to their social and ecological conditions (Stone, 2007).

Considerable attention has been given to farmer knowledge and practices related to the evolution of resistance in weeds and insects in GE cropping systems (Llewellyn and Pannell, 2009; Mortensen et al., 2012; Ervin and Jussaume, 2014). In the United States, survey data from 2005–2006 revealed that most farmers were unaware that glyphosate-resistant weeds were evolving or that their actions were contributing to this evolution (Johnson et al., 2009). In contrast, a survey of Iowa farmers showed that as of 2012 nearly one-third were aware that they had fields with weeds resistant to glyphosate and just over one-tenth indicated that corn rootworm (*Diabrotica* spp.) resistant to *Bt* was in their fields (Arbuckle, 2014). Most of the surveyed farmers relied on and trusted their chemical dealers when faced with weed and insect-pest problems far more than they relied on or trusted any other source of knowledge, including the U.S. Department of Agriculture (USDA) and university extension services. In the case of Iowa, most farmers surveyed saw resistance as inevitable; this is not ideal for implementing "widespread, coordinated pest management practices and strategies" for slowing pest resistance (Arbuckle, 2014:7). Arbuckle (2014) expressed concern because those findings indicated a sense of powerlessness and a lack of knowledge, whereas the evolution of resistance could at least be slowed with widespread and coordinated efforts. However, the author concluded that Iowan farmers were ready to engage in coordinated resistance-management strategies that would involve an array of actors, including the private sector, commodity groups, farmers, and university personnel (Arbuckle, 2014).

Several studies have emphasized the importance of incorporating farmers into weed and insect pest-management programs (Tripp, 2009a; Ervin and Jussaume, 2014). Ervin and Jussaume (2014:407) stressed that weed-management programs must address the human dimensions to slow herbicide-resistant weeds, noting that most programs ignore sociological variables, including "the nature and strength of community ties (such as shared grower perceptions of what is going on in their fields), shared personal values (for example, attitudes towards evolution, environmental stewardship, and neighboring farmers' well-being), and the ways in which farms are incorporated into financial hierarchies (whether farmers have outstanding bank loans)."

Mortensen et al. (2012) warned that weed management in agriculture demands the need for knowledge-intensive approaches among farmers. Reliance on single or simple technologies (such as HR crops) does not provide such an approach. In the case of HR crops, overcoming the enticement of the short-term economic advantages of using one herbicide to instead focus on long-term economic benefits is one of the larger changes for mitigating the evolution of resistant weeds (Ervin and Jussaume, 2014).

Overall, the study of the effects of GE crops on farmers' skills and the interaction of farmer knowledge with GE crops remains limited to a few studies in specific locations. A more systematic study of farmer knowledge is needed to improve the regulatory structures in which farmers function and to value and preserve farmers' skills and capabilities. There is clear evidence that farmers' participation in and knowledge of weed and insect-pest management is important for slowing the evolution of pest resistance in fields (Mohan et al., 2016).

FINDING: There is some evidence suggesting that farmers have insights helpful to regulators of GE crops but that regulators do not make use of this knowledge.

FINDING: A few studies have suggested that HR and *Bt* crops contribute to farmer deskilling.

RECOMMENDATION: More research to ascertain how farmer knowledge can help to improve regulations should be conducted. Research is also needed to determine whether and to what degree genetic-engineering technology in general or specific GE traits contribute to farmer deskilling.

Gender

Few studies have explicitly focused on GE crops and gender (Chambers et al., 2014), although attention given to women and gender in the food system has increased since the 1970s. Women made up 20 percent of the agricultural labor force in Latin America, over 40 percent in Asia, 50 percent in sub-Saharan Africa, and 43 percent in all developing countries in 2010 (FAO, 2011). Women are also being integrated as low-cost "skilled" labor into export value chains (FAO, 2011). In the United States, Australia, and New Zealand, the proportion of women in farming grew between 1980 and 2010, though the proportion of women involved in agriculture declined in Japan and throughout Europe in general (FAO, 2011). As research has focused on women, the emphasis placed on understanding gendered agricultural production systems has expanded. A gendered analysis allows for recognition that agricultural practices undertaken by women and men differ in diverse locations, and these differences need to be acknowledged when conducting agricultural research and development (Bock, 2006).

The research on gender and genetic engineering in agriculture has focused primarily on developing countries (Bennett et al., 2003; Subramanian and Qaim, 2010; Zambrano et al., 2012, 2013). However, on the basis of previous analyses of gender and agriculture (for example, Feldman and Welsh, 1995; Schafer, 2002; Sundari and Gowri, 2002; Prugl, 2004), there is little doubt that gender is relevant to the adoption, production, and marketing of GE crops in both developed and developing countries. Scholars have consistently found that women are often uniquely constrained in their production practices; these constraints limit female producers' abilities to enhance their incomes and, in subsistence-farming households, to improve household food security. There are constraints on access to education, information, credit, inputs, assets, extension services, and land (Ransom and Bain, 2011; Quisumbing et al., 2014). Although the roles of women in agriculture in developed countries may differ from those of women in developing countries, the constraints on female producers have many similarities. Not unlike women in developing countries, women in developed countries have historically been marginalized from farming by being denied access to the material resources needed for success, such as land, labor, and capital (for example, Leckie, 1993). Those gendered constraints are probably relevant to GE crops.

One major theme that has emerged from the few studies that have been done is that commercialized GE crops differentially affect men and women depending on the gendered division of labor and cultural roles. For example, in India, it was found that female laborers benefited from the increased work hours—and thus increased income—associated with increased yields from *Bt* cotton because women pick the cotton (Subramanian and Qaim, 2010). Conversely, male laborers generally spray chemicals, so they saw a reduction in their labor time. Similarly, a study of 32 small-scale farmers in the Makhathini Flats of South Africa found that the planting of *Bt* cotton was beneficial for women in the household; in this case, it was because women did not have to spray the crops, so their energies could be diverted to other activities (Bennett et al., 2003).

In Burkina Faso, fewer insecticide applications were needed for *Bt* cotton and that meant women spent less time in fetching water (Zambrano et al., 2013). In Bolivian households that adopted HR soybean, the second major contributor to production in the household—often the wife—had more time to work off the farm (Smale et al., 2012). Female farmers in Colombia who adopted *Bt* cotton preferred IR varieties because they reduced the number of laborers needed, whereas men reported that *Bt* cotton increased yields and overall benefits (Zambrano et al., 2012). In contrast, HR cotton in Colombia resulted in the hiring of fewer women for weeding, traditionally a female task (Zambrano et al., 2013). Female maize farmers in the Philippines, whether they grew *Bt* varieties or not, reported that *Bt* saved labor, but men who planted maize did not note a time-saving aspect to either *Bt* or non-*Bt* varieties (Zambrano et al., 2013).

Another theme that has received some support in the literature on GE crops in commercial production is the role of women in decision-making in farming households. In Colombia, in the case of *Bt* cotton, women were found to participate with men in decision-making and supervision of *Bt* cotton. Similarly, in the Philippines, women and men reported that they collaborated in most activities related to *Bt* maize, including decision-making (Yorobe and Smale, 2012; Zambrano et al., 2013). The increasing importance of women in decision-making in farm households is further supported by other, non-GE focused research. It has been observed in Australia that women's involvement in decision-making about planting new crop varieties and soil conservation has increased in farm households (Rickson et al., 2006).

The issue of gender-appropriate technologies is also relevant to GE crops. In many regions, specific types of agricultural technologies are associated with masculinity; for example, large machinery, such as tractors, is usually seen as falling within the male domain (Brandth, 2006). However, GE crops may fit within more traditionally female-associated technologies. In specific regions, such as the United States and Europe, female farmers tend to be concentrated in alternative agricultural systems (Chiappe and Flora, 1998; Peter et al., 2000; Rissing, 2012). What makes that relevant to GE crops is that many of the alternative agricultural systems, particularly in developed countries, have not used GE crops, primarily for philosophical reasons (Rissing, 2012) or, in the case of USDA organic certification, because of the outright restriction on using GE crops. In both developed and developing countries, women are more likely to farm on a smaller scale (SOFA Team and Doss, 2011; Hoppe and Korb, 2013). Therefore, although GE crops are more likely to be considered a female-appropriate or gender-neutral technology, the types of farming systems of which women are the primary farmers tend not to have high adoption rates for GE crops.

FINDING: GE crops with *Bt* and HR traits differentially affect men and women in the agricultural labor force, depending on the gendered division of labor for the specific crop and for particular localities.

FINDING: There is a small body of evidence that women's involvement in decision-making about planting new crop varieties and soil conservation has increased in farming households in general, including households that have adopted GE crops.

Rural Communities

The connection between changes in agriculture and their effects on communities, particularly rural communities, has received scrutiny among social scientists for decades in the United States. The Goldschmidt thesis, completed in 1948, argued that industrial agriculture adversely affects the quality of life in rural communities (Carolan, 2012). Much more recent research in the United States continues to find support for the general thesis, although the causal mechanisms that drive such outcomes remain under debate (Lyson et al., 2001; also see Lobao and Stofferahn, 2008, for summary of 51 studies). The implication of the Goldschmidt thesis is that if the adoption of particular technologies contributes to further industrialization of the farming sector, with increased consolidation and decreasing family farms, there will probably be deleterious consequences for rural communities.

Specific to the present report is the concern over how GE crops and genetic engineering affect communities. Few studies have focused explicitly on commercialized GE crops and communities, but inference can be drawn from other studies that have focused on the intersection of agricultural technologies, farm organizations and scale, and communities (Lobao and Stofferahn, 2008). As a previous National Research Council report (NRC, 2010a:12) concluded, “Research on earlier technological developments in agriculture suggests that there are likely to be social impacts from the adoption of GE crops.” The extent of the social effects of the introduction of GE crops is unclear, in part because little research has addressed the subject, but effects may include changing “labor dynamics, farm structure, community viability, and farmers’ relationships with each other” (NRC, 2010a:3). Social and economic consequences related to commercialized GE crops are not inherently new or unique but rather contribute to changes that have been seen after previous technology adoption (NRC, 2010a). Thus far, the small numbers of studies that touch on community effects of GE crops tend to focus on adverse effects, such as reduced employment for weeding, as discussed above in the section “Gender.” However, because of the lack of attention to measuring change at the community and household levels, it is difficult to draw any overarching conclusions related to specific GE crops or to genetic engineering in general and community and household effects.

Seed Availability and Cost

There is some evidence of a correlation between the substantial rise in the amount of land planted with GE crops and a decline in the amount of non-GE seeds used (Pechlaner, 2012). The availability of non-GE varieties for purchase and planting by farmers in the United States declined by 67 percent for maize, 51 percent for soybean, and 26 percent for cotton from 2005 to 2010 (Heinemann et al., 2014). A number of explanations for these declines are possible. The committee reviewed publicly available maize hybrid trials in three of the top four maize-producing states in the United States (Iowa, Illinois, and Minnesota; Nebraska is ranked third in the value of maize crop, but the trial results do not differentiate GE and non-GE hybrids). In 2014 in the three states, 86 non-GE hybrids were tested compared with 544 GE hybrids (13.7-percent non-GE, 86.3-percent GE). The prevalence of hybrids with stacked GE traits is illustrated in the results from Minnesota: of the 219 GE hybrids tested, 198 contained two or more GE traits, and only 21 contained solely the HR trait for glyphosate

(90.4 percent of the hybrids contained stacked GE traits). Observations in Brazil also show a decline in the availability of non-GE maize hybrids (from 302 to 263) and an increase in GE maize hybrids (from 19 to 216) from the time when GE maize was approved in 2008 to 2012 (Parentoni et al., 2013).

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. However, there is uncertainty about the rate of progression of the trend. The general trends indicate that nonadopters and partial adopters of GE varieties had fewer choices for hybrids or varieties in 2015 than they did before GE crops were introduced. That was also demonstrated by Krishna et al. (2016), who assessed varietal diversity available to cotton growers in India, representing full adoption, partial adoption, and nonadoption of *Bt* cotton.

More research is needed to ascertain whether a change in varietal diversity and availability of all crops in all countries has occurred.

For farmers who want to grow GE crops, the cost of GE crops may limit their adoption by smallholders, particularly resource-poor smallholders. The price of GE crop seeds tends to be higher than that of other types of seed. That limitation is binding only if the seed price is not compensated for by higher net income, for example, through reduced insecticide applications, reduction in damage to yields, or saved labor. The important point is what percentage of total costs seed represents and how a farmer recovers this cost. In most situations, seed cost is a small fraction of total costs of production, although it may constitute a financial constraint because of limited access to credit. In addition, small-scale farmers may face a financial risk when purchasing a GE seed upfront if the crop fails; this may be a substantial risk consideration for small-scale farmers.

Finger et al. (2011) found that seed cost for *Bt* cotton was significantly higher than that for non-GE cotton in South Africa, India, and the United States but not in China. The difference between the price of non-GE seed and the price of *Bt* cottonseed was 97 percent in South Africa, 222 percent in the United States, and 233 percent in India. The authors noted that there had been a change in government policy in India since the time when many of the studies included in their meta-analysis were conducted. The Indian government invested in the market in 2006, and this lowered the price difference between *Bt* and non-*Bt* to 68 percent. In the same study, *Bt* maize seed was 9.9 percent more expensive than non-*Bt* seed in Spain, 17 percent more expensive in Germany, and 36 percent more expensive in Argentina (Finger et al., 2011). The price of seed appeared to be influenced by the region within a country and the extent of infestation by the target insect pest. That is, the price of *Bt* seed was lower where target insect-pest populations were small and *Bt* varieties were less likely to close the gap between actual and potential yields. In a 2010 survey of maize farmers in the Philippines, Afidchao et al. (2014) reported that seed costs were 60 percent higher for all GE maize types (*Bt*, HR, and *Bt*-HR) than for non-GE maize. Some initiatives have attempted to address cost through humanitarian-use licenses that allow researchers to develop GE crops without concern about having to pay royalty fees to agricultural biotechnology firms (Takeshima, 2010).

Coexistence

Because of producer and consumer preferences, GE crops have been separated into different supply chains from non-GE crops that may be produced with synthetic fertilizers and pesticides and non-GE crops that are cultivated with practices that meet standards set for organic production.[16] GE crops and nonorganic, non-GE crops both may use synthetic fertilizers and pesticides, so USDA distinguishes them as GE conventional production and non-GE conventional production; the third category is known as organic production (Greene et al., 2016). To simplify terminology, the committee will refer to the production process that uses GE seed as "GE," the production process that may use synthetic inputs but not GE seed as "non-GE," and the production process that uses organic practices as "organic."

The separation begins on the farm, where efforts are made to prevent gene flow between GE crops and non-GE or organic varieties of the same species and between GE crops and related plant species such as wild relatives. Efforts are also made to keep seed separate so that producers have a choice of kind of seed to grow (organic, non-GE, or GE) and markets to sell to. When crops leave the farm, different supply chains exist for each production system.

Managing and maintaining separation among three production processes is known as coexistence. It is a particular issue for farms in the United States, where all three production processes occur, sometimes close to one another. Coexistence issues on the farm are also present in other countries that grow GE crops, but the United States is the best example in that it grows more hectares of GE crops and more species of GE crops than any other country. Therefore, much of the literature and experiences discussed in this section are based on the United States, although the findings are likely to be applicable to other locations.

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[16] In the United States, *organic* is a process-based certification granted by USDA's National Organic Program (NOP). Among other metrics, organic growers may not use synthetic insecticides or herbicides or GE seeds to produce their crops, and they must take reasonable steps to prohibit the presence of GE content in the final product. Because the certification is process-based, NOP does not specify a tolerance level of GE content. In other jurisdictions, such as the EU, food produced organically can be rejected as organic if test results show GE content beyond a set threshold.

Coexistence is not an issue that has only appeared since GE crops were commercialized. Farmers growing high-value specialty crops—such as popcorn, soybean for tofu, and low-linolenic acid canola—have long protected their crops from accidental mixing with lower-value crops to prevent adventitious presence. Farmers who grow crops for seed production also isolate their crops from related crops to ensure the purity of the seed variety and thereby avoid adventitious presence. With regards to agriculture in general, *adventitious presence* refers to unintended low levels of impurities in seeds, food, feed, or grains from crops.

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. This unintended and accidental presence can be introduced to organic or non-GE crops in the field in several ways. Pollen from GE crop fields has the potential to cross-pollinate nearby non-GE crops of the same species or of a related species. GE seed can be accidentally mixed with non-GE seed; planting of the intermixed non-GE seed would lead to the growth of some plants with GE traits in the field. Seeds with GE traits left over from the previous season can germinate in a field that has been planted with non-GE seed in the following season.

Preventing adventitious presence is valuable for social reasons.[17] Farmers want the freedom to decide what crops to grow based on their skills, resources, and market opportunities. That freedom can be constrained by adventitious presence from nearby farms that use a different production process.

Preventing adventitious presence is also important for economic reasons. First, seed—whether organic, non-GE, or GE—commands a higher price (that is, a price premium) compared to bulk grain, so it is critical for the farmer's bottom line that its purity be maintained regardless of the crop's method of production.[18] Farmers of seed and high-value crops have put identity-preservation systems in place to help to ensure purity, and they need the price premium to help to pay for these systems (USDA Advisory Committee, 2012).

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[17] Environmental issues related to adventitious presence were discussed in Chapter 4.

[18] For example, seed companies of crops with GE traits and farmer trade associations have developed programs, guidelines, and best management practices to reduce the incidence of unwanted low-level presence of GE traits. Companies have sponsored the Excellence Through Stewardship Program, which develops best management practices to prevent gene flow during testing and field trials of GE crops and to minimize inadvertent introduction of unwanted GE traits (Excellence Through Stewardship, 2008, updated 2014). The American Seed Trade Association has guidelines to ensure the production of high-quality seed stock and to comply with certification standards developed by the Association of Official Seed Certifying Agencies and the International Seed Testing Association.

Second, at the other end of production, the segregation of end-use markets for organic, non-GE, and GE crops because of consumer preferences has created a price premium for organic and non-GE crops. A meta-analysis by Crowder and Reganold (2015) indicated that the global price premium related to a variety of organic crops ranged from 29 to 32 percent but that organic crops cost more to grow (because of higher labor inputs and lower yields) than nonorganic crops. Therefore, higher price premiums are critical for the profitability of organic farmers. USDA's Economic Research Service (ERS) reports that U.S. organic maize and soybean prices are generally two to three times higher than the price of non-GE varieties (Greene et al., 2016).

BOX 6-5
Who is Responsible for Costs Caused by Unwanted Gene Flow?

Minimizing unwanted gene flow from nearby crops requires expenditures on management practices, such as the creation of buffer zones between fields of organic or non-GE crops and those of GE crops. In the United States, there is disagreement about who is responsible for paying for the management practices and who is liable for damages if a grower of organic or non-GE crops loses a market price premium because of the presence of GE traits. Should the responsibility to prevent gene flow fall on the GE crop farmer or the farmer of organic or non-GE crops? The issue of liability has not been settled in the United States by state or federal law or by litigation (Endres, 2008; Endres, 2012).[a] As a matter of practice, USDA's National Organic Program places the burden of avoiding gene flow from GE crops on the organic producer; evidence suggests that this is equally true for the producer of non-GE crops (NRC, 2010a; Endres, 2012).

An advisory committee convened by the U.S. Secretary of Agriculture to address possible compensation or crop-insurance mechanisms related to coexistence failed to reach agreement in 2012 (USDA Advisory Committee, 2012). Some on the advisory committee argued that because foods marketed as organic or non-GE can be sold at a market premium, it is up to the growers and distributors of those foods to take whatever steps are needed to meet the standards and protect the foods from commingling with GE varieties. Those supporting that argument pointed to identity-preserved crops, such as sweet corn and low-linolenic acid canola, which enjoy market premiums over bulk commodity maize and industrial rapeseed. It was argued that growers who seek to market such high-value specialty crops should bear the costs of protecting their unique qualities by carefully segregating them throughout the growing and distribution chain. Furthermore, such growers voluntarily take a risk by agreeing to private contracts with low thresholds of the presence of GE content and therefore should bear the burden of the costs of meeting those requirements. In contrast, growers of organic and non-GE crops posited that the burden should be placed on the newer genetic-engineering technology to avoid harm to existing older farming practices. They

To protect that premium and because of USDA's National Organic Program requirements, organic farmers in the United States take measures to prevent adventitious presence, such as planting buffer strips or taking land that borders a GE crop field out of production (Box 6-5). Farmers of non-GE crops may do the same to avoid cross-pollination from neighboring GE crop fields. There is a growing demand for food and feed from non-GE crops, particularly in countries in which there is strong consumer opposition to GE products, few if any GE crops have been approved, or GE foods must be labeled. Depending on supply and market demand, non-GE crops may carry a market price premium. In late 2015, USDA–ERS reported non-GE price

drew analogies to the harm caused by drift of herbicides and insecticides into neighboring fields when those chemicals were introduced. All the parties agreed that farmers should have the right to use production systems of their choice and that the key to avoiding conflicts was to encourage greater communication among farmers. However, the advisory committee ultimately could not agree on which parties should be responsible for bearing the costs of compensation or on a crop-insurance mechanism to encourage successful coexistence (USDA Advisory Committee, 2012).

In the European Union (EU), coexistence rules are the responsibility of member states. EU guidelines recognize the right of farmers to use production practices of their choice, including approved GE varieties, and recommend that coexistence rules be no more stringent than needed to ensure that non-GE and organic farmers can produce crops in compliance with the EU standard, which requires a product to be labeled if it contains more than 0.9-percent content derived from GE crops (EC, 2009). In all member states that have adopted segregation measures, the burden is on GE crop growers and operators to avoid gene flow to neighboring farmers (EC, 2009). However, practical experience with EU coexistence measures has been limited in that only two GE crops have been authorized for cultivation, and only a few EU countries have cultivated GE crops. Some member states have taken the position that the only way to ensure that non-GE and organic farmers can meet the 0.9-percent standard is to ban cultivation of GE crops in their regions. That position was given more weight by a 2014 EU decision that allows member states more freedom to decide whether to cultivate GE crops in their countries.

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[a] Although USDA's Animal and Plant Health Inspection Service has not required inclusion of coexistence measures in its deregulation decisions, it is nevertheless required to consider the effects on non-GE farmers as part of its environmental assessment under the National Environmental Policy Act (NEPA) as a result of court decisions (*Geertson Farms v. Johanns*, 2007). In *Center for Food Safety v. Vilsack* (2013), however, the U.S. Court of Appeals for the Ninth Circuit agreed with USDA that, once it had determined that a regulated article was not a plant pest within the meaning of the Plant Protection Act, USDA no longer had legal authority to impose continuing requirements or to consider alternatives to unconditional deregulation under NEPA, even if such alternatives would be environmentally preferable.

premiums for food soybean 8–9 percent higher than average food-soybean prices and 12–14 percent higher for non-GE soybean for feed (Greene et al., 2016). As a result, growers in the United States and in other agricultural export regions around the world may decide to meet such demand by avoiding GE seed and growing their crops to meet the required regulatory and market specifications for non-GE crops.

Third, prevention is important because cross-contamination among crops from the three production processes has economic costs. In the United States, the organic certification is process-based, so low-level presence of GE content in organic food products does not threaten a grower's certification or prevent the end product from being marketed as "USDA organic" (USDA–AMS, 2011). However, the private sector may impose standards that go beyond USDA's requirements. U.S. food retailers, restaurants, and food manufacturers are requiring non-GE supplies for "non-GMO" marketing and labeling campaigns (for example, Schweizer, 2015; Strom, 2015). Through contract requirements, growers of organic or non-GE crops may have to supply products that do not exceed a threshold of GE content set by a private company, a strict market (for example, the EU), or a voluntary certifier (for example, the Non-GMO Project, a private voluntary certifier). The grower bears the risk of losing the market premium if the supplied crop is rejected because it does not meet a contractually established standard. However, because contracts between growers and buyers are private, it is difficult to find documented information about how extensively growers are contracting to meet specific non-GE standards or to what extent farmers of organic or non-GE crops are incurring economic losses as a result of being unable to meet contracts because of cross-contamination. In 2016, USDA–ERS released a survey that showed that the percentage of organic farmers reporting economic losses due to the unintended presence of GE materials in their crops varied by region and by the presence of GE crop varieties in their area. In Illinois, Nebraska, and Oklahoma, 6–7 percent of organic farmers reported losses; on a national level, 1 percent of all certified organic growers in 20 states reported losses, including expenses for preventive measures and testing, in 2011–2014. Those losses were estimated at $6.1 million (Greene et al., 2016). USDA–ERS stated that the percentage of organic farmers reporting economic losses would probably have been higher had the study been limited to organic farmers growing crops with a GE counterpart, instead of all organic farmers.

Another economic cost that can be connected to coexistence is the management of seed rights. GE seed is protected by patents and by legal agreements between seed sellers and buyers that restrict the grower's use of the seed, including prohibitions on seed saving and resale (for more discussion of patents, see section "Intellectual Property" below). An economic conflict can occur if a farmer who has not purchased GE seed discovers that gene flow from other farms has caused GE traits to be mixed in with his or her crops. Farmers could be legally liable for patent infringement if they knowingly use GE traits in their fields for which they have not paid (Kershen, 2003).

Despite the acknowledged difficulties of managing the coexistence of different agricultural production processes in a geographic area and questions related to responsibility and liability (Box 6-5), the evidence indicates that many areas are successfully growing organic, non-GE, and GE crops. Carter and Gruère (2012) demonstrated that countries producing the four most widely grown GE crops (maize, soybean, cotton, and canola) are also still producing and exporting non-GE and organic varieties to meet global niche-market demand (Table 6-1). Gruère and Sengupta (2010) have documented how South Africa provides for a non-GE maize identity-preservation program even though most growers plant GE varieties.

A particularly difficult challenge for coexistence arises from the situation in which a GE trait that has not received *any* regulatory approval is accidentally released into the food supply. The unapproved GE trait may

TABLE 6-1 Successful Coexistence Schemes in Selected Countries That Produce and Market Genetically Engineered (GE) and Non-GE Crops[a]

Producing Country	Maize	Soybean	Cotton	Canola
Australia			GE and organic	GE and non-GE
Brazil	GE	GE and non-GE	GE and organic	
Burkina Faso			GE and organic	
Canada	GE, non-GE, and organic	GE, non-GE, and organic		GE, non-GE, and organic
China			GE and organic	
India			GE and organic	
Pakistan			GE and organic	
South Africa	GE and non-GE	GE	GE and organic	
Spain	GE, non-GE, and organic			
United States	GE, non-GE, and organic	GE, non-GE, and organic	GE and organic	GE, non-GE, and organic

[a] Non-GE crops include those produced with synthetic fertilizers and pesticides and those produced with practices that meet organic standards. The former is described in the table as "non-GE", the latter as "organic."

SOURCE: Carter and Gruère (2012).

escape from field trials through gene flow to neighboring crops of the same species, or, more typically, the seeds of the variety being tested may be commingled with the seeds of non-GE crops or commercialized GE crops. When such accidental releases are detected, they can lead to both domestic market turmoil and international trade disruptions. All growers of the same crop in which the unapproved trait has been found—whether GE, non-GE, or organic—will face substantial costs of testing to ensure that the unapproved trait is not present in their production. If the unapproved trait were discovered at any level, the food or feed would have to be destroyed because the sale of any food or feed with an unapproved GE trait would be unlawful. Such incidents also disrupt trade because importers are unlikely to want to buy crops with any levels of GE traits that have not yet been approved for commercialization. Examples of such market disruptions include:

- The detection of an unapproved HR trait in U.S. rice supplies, which led to the closure of EU markets to rice imports from the United States. U.S. rice producers and exporters experienced losses at the time and a loss in their share of the EU market to other exporting countries. EU rice importers suffered substantial losses "because of the need to recall products from the supply chain, the higher costs due to additional testing, the disruption to the rice supply and the damage to their brands" (Stein and Rodríguez-Cerezo, 2009:20).
- The closure of Japanese and South Korean markets to U.S. soft white wheat due to the discovery of unapproved HR wheat in Oregon. The markets were closed even though no HR wheat was found in the commercial wheat supply (Cowan, 2013).

FINDING: Strict private standards mean that producers may meet government guidelines for adventitious presence but fail to meet private contract requirements.

FINDING: The question of who is economically responsible for adventitious presence is handled differently by different countries.

SOCIAL AND ECONOMIC EFFECTS BEYOND THE FARM

When crops leave a farm, they may end up in a market just down the road, a livestock feedlot, or a barge headed to a market on the other side of an ocean. Most GE crops commercially available in 2015 were bulk commodity crops traded worldwide, but even GE specialty crops, such as papaya, are exported. Thus, commercialized GE crops intersect with consumers, the international trade regime, and the global food-distribution system. The extent to which they are developed and grown is influenced by intellectual-property rules and regulatory-system costs.

Consumers' Acceptance and Marketplace Awareness

The analysis of consumers' acceptance and purchasing intention for food derived from GE crops has been the focus of several studies in the last two decades. Those studies have relied on survey research, choice experiment, and hedonic analyses among other methods (see Costa-Font et al., 2008; Frewer et al., 2011; Rollin et al., 2011). More than 100 studies on consumers' willingness to pay (WTP) for food derived from GE crops in over 20 countries have been conducted. WTP estimates whether (and if so, how much) price premiums are necessary for consumers to use or avoid a GE crop. Colson and Rousu (2013) summarized the state of the literature on WTP, including work conducted by Lusk et al. (2005), Dannenberg (2009), and Lusk (2011). They found that consumers' WTP for food derived from GE crops is lower than that for food with no ingredients from GE crops and that the magnitude of the consumers' discount for food from GE crops depends on the type of genetic change made, the type of food product, and how the genetic change altered the final product. They also reported that U.S. consumers were more accepting of food derived from GE crops than were European consumers. Along similar lines, Colson and Huffman (2011) found that consumers' WTP was influenced by the information available to them when they made their decisions. Information that highlighted the benefits of genetic-engineering technology increased the WTP for food derived from GE crops. Phillips and Hallman (2013) concluded that consumers assess food from GE crops on the basis of how the food is presented—that is, whether the food presents benefits or risks—but that the assessments vary when levels of consumers' pre-existing knowledge and other factors are taken into account.

Colson and Rousu (2013) raised important questions about the existing literature and its limitations. Specifically, WTP studies may not shed much light on consumer acceptance because most consumers are not aware that food derived from GE crops is available in the marketplace. The authors also questioned the variability in the results of the studies that they reviewed and the ability of such studies to reflect consumers' behavior when they make purchases.

Research has also been conducted in several countries on the question of labeling foods derived from GE crops.[19] Polls conducted in United States in the last 15 years have shown growing support for labeling among the American public, from 86 percent saying "yes" to requiring labels in 2000

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[19] For a discussion of labeling policies for GE foods, see Chapter 9.

to 93 percent in 2013 (Runge et. al, 2015). A 2006 survey conducted in one city in India, with a complementary Internet survey, found that over 90 percent of respondents considered labeling as somewhat or very important; however, support fell to around 60 percent when costs associated with a 5-percent rise in prices due to labeling were introduced to the question (Deodhar et al., 2007). A 2015 poll in Canada reported that 88 percent of Canadians wanted mandatory labeling of GE foods (CBAN, 2015); voluntary labeling was already in place at the time. When mandatory labeling of GE foods went into effect in Taiwan in 2001, 83 percent of those surveyed were in favor of it (Ganiere et al., 2004). Labeling of foods derived from GE crops has been in place in the EU since 2001. There is no international standard for labeling. The Codex Alimentarius Committee on Food Labeling reached an impasse in 2011 on developing guidelines and standards for labeling GE foods, leaving the issue up to Codex members to consider approaches to labeling "consistent with already adopted Codex provisions" (CAC, 2011).

Labeling can be required by a governmental body or can be voluntary. In the United States, the U.S. Food and Drug Administration (FDA) has the authority to require label information to ensure the safe use of a product or to prevent marketplace deception; because FDA has determined that all commercialized GE crops are not materially different from conventionally bred crops, it has not found cause to mandate labeling of GE foods under its authority (see Chapter 9).

A mandatory label requiring the disclosure of GE content in food imposes costs on food manufacturers, some of which could be passed on to consumers in the form of higher prices (Golan et al., 2000). Claimed estimates of the total costs of mandatory labeling of foods derived from GE crops vary widely, depending primarily on whether short-term or long-term costs are included. Short-term costs are those associated with changes in labels and marketing efforts. Long-term costs are those associated with changes in the value chain and markets that result from the implementation of a labeling policy. They may include expenses related to segregation, traceability, and identity preservation of products and reorganizations of value chains. For example, a general retail mandatory-labeling model by FDA considers the short-term cost of one-time changes in retail labels, such as UPC codes and product labels (Muth et al., 2012). The model finds that the cost of new labeling requirements decreases over 42 months; at that point, label changes could be accommodated within the normal business cycle "at minimal additional cost." The need to reprint labels is likely to entail a relatively trivial cost, which by itself would be unlikely to affect consumer prices (Shepherd-Bailey, 2013).

Estimated costs of mandatory labeling of GE foods are considerably higher, however, if longer-term market-response scenarios are included.

If required to label, manufacturers would probably reformulate products to avoid labeling by using non-GE ingredients where possible instead of putting on a label that will lead to a loss of sales. In the EU, most food manufacturers have reformulated their products to avoid having to label their products under the EU mandatory-labeling regime (Wesseler, 2014). The time and expense of reformulating products and the use of substitutes for GE ingredients would entail additional costs. Furthermore, if a company reformulated its products to avoid labeling, it would still be required to test each of its ingredients for GE content to ensure that it was complying with labeling requirements. How difficult and expensive that task would be depends largely on the level at which tolerances of GE content were set before labeling would be required. Maintaining adequate segregation to achieve the EU level of 0.9 percent would be much more expensive than, for example, meeting a 5-percent tolerance level.

Cost estimates that include testing, segregation, and identity preservation vary widely. Comparisons are difficult because assumptions are often unstated; indeed, Teisl and Caswell (2003:16) noted in their review of cost studies that estimates range "from very modest to significant increases in costs" in part because of different assumptions and different kinds of costs. One market response would probably be downstream market pressure on farmers to grow non-GE crops to supply food manufacturers with materials that would enable them to avoid labeling; an increase in non-GE sources could lead eventually to a decrease in ingredient costs.

The benefits of mandatory labeling depend on the extent to which consumers use the information to choose products that they want (or avoid ones that they do not want) and on their WTP for such attributes. The assumption is that consumers would use the information to avoid food derived from GE crops, although the percentage of consumers who would do so is likely to differ from country to country. Most of the economic studies that compared a mandatory-labeling requirement of GE foods with a voluntary "non-GE" label have concluded that a voluntary "non-GE" label is a more efficient way to provide information to consumers and to permit consumer choice. However, that analysis considers all consumers to be uniformly affected. Gruère et al. (2008) argued that mandatory labeling is less likely to lead to expanded consumer choice in that companies are likely to withdraw products with GE content from the market because consumers are assumed to ascribe an adverse connotation to the label.

Ultimately, of course, countries may choose policies that favor values other than economic efficiency, including consumer "right-to-know" policies that express preferences for consumer autonomy and fairness. For example, if non-GE labeling is voluntary, many products would have no label information about GE content. Consumers would not know whether the product contained GE ingredients and so would be deprived of the ability to make an informed choice about each product. Mandatory labeling provides the opportunity for consumers to make their own personal risk-benefit decisions (regardless of the regulatory determination of safety) and to express a preference for a method of production. A voluntary non-GE label places the burden on consumers who want to avoid GE foods to search for non-GE products and provides no information to consumers who may not be actively searching for the information but who might be informed by the label. Voluntary labeling also may not help consumers who cannot afford the kinds of foods that will be voluntarily labeled.

FINDING: Consumers' willingness to pay for non-GE food is price-sensitive.

FINDING: The economic effects of mandatory labeling of GE food at the consumer level are uncertain.

Constraints on Trade

Starting in the 1980s, global trade in agriculture has become more liberalized through a series of international free-trade agreements, including those negotiated under the World Trade Organization. Although harmonization of standards has advanced, there remain issues or products that countries do not treat in the same way and about which they have disagreements. The disagreements, some of which are related to genetic engineering in agriculture, have economic implications.

GE crops are approved by national governments, not by an international body or under an international agreement. This approach is logical and appropriate; countries should have sovereignty over regulatory decisions. However, making regulatory decisions at the national level creates a situation in which a GE crop may have been approved for production in one country but has not yet been approved for importation into another. Alternatively, the GE trait–crop developer might not seek regulatory approval in importing jurisdictions, which raises the possibility that a product approved in one country may inadvertently reach a different country where the product has not been approved. These two situations are known collectively in the international trade and regulatory literature as asynchronous approval[20] (Stein and Rodríguez-Cerezo, 2009; Gruère, 2011; Henseler et

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[20] There is no unified definition of the term asynchronous approval; different countries and organizations have similar but not the same definition (FAO, 2014). The committee recognizes that the term *asynchronous approval* can be framed within a policy discourse context and that it may have some different interpretations by different audiences. However, this is the term of art used in the literature examining trade and regulatory issues with varying definitions.

al., 2013). The consequence of asynchronous approval is that exports of crops with GE traits must be segregated from exports of non-GE crops so that exporters only send non-GE crops or GE crops that have been approved into the importing jurisdiction. The presence of unapproved GE crops in non-GE crop imports could cause a shipment to be rejected, which incurs costs. Therefore, a segregated export supply chain must be maintained, which also adds expense and requires testing and segregation systems to keep GE crops out of shipments intended for import markets that have not yet approved the GE crops (Box 6-6).

If maintaining testing and segregation systems is not economically feasible, trade of the product in question between two countries may cease. Before 1997, the United States shipped 4 percent of its maize exports to the EU; by 2004, the EU share of U.S. market exports were less than 0.1 percent because U.S. maize growers were planting GE varieties not approved in the EU (PIFB, 2005). GE papaya from Hawaii could not be exported to Japan between 1998 and 2011 because the top Japanese importer would not accept GE papaya; during that period, Hawaii went from supplying 97 percent of Japan's papaya imports to less than 15 percent (VIB, 2014).

Asynchronous approvals can also have multisector effects tied to restriction on imports and increases in costs and price. The EU is a large importer of soybean, predominantly to feed its livestock. The United States, Brazil, and Argentina dominate the export market for soybean for livestock feed, and almost all soybean produced in these countries has GE traits. A 2007 European Commission report modeled the effects of trade disruptions between the EU and its livestock-feed suppliers. The EU supplies much of its own maize, so the effects of trade disruptions due to asynchronicity in that crop would not be substantial. However, if the EU lost soybean imports from the three largest suppliers at the same time because of asynchronicity, the price of soybean and soymeal would increase by over 200 percent in the following year or two. It would be difficult for farmers to respond quickly with substitute feeds, so the number of livestock in the EU would decrease. The decrease in numbers would persist over a long term wherever substitute feeds could not be supplied. The decline in livestock would have substantial adverse effects on a sector that represents 40 percent of the EU's agricultural production (LEI et al., 2010).

Finally, asynchronous approvals may deter the development and adoption of new GE traits or new GE crops because farmers producing for an export market may be reluctant to grow varieties that incur the risk of not gaining regulatory approval. For example, in the mid-2000s, U.S. wheat farmers' concern about acceptance of HR wheat by export markets led them to reject the variety that Monsanto was developing; as a result, Monsanto withdrew the product (Schurman and Munro, 2010). Developers also may delay the commercialization of a new GE crop until it has been

BOX 6-6
Testing for the Presence of Genetically Engineered Traits

Food traceability systems, identity preservation, and sensitive and reliable tests are needed to ascertain whether imports contain GE content (Bonfini et al., 2002). The same testing methods can be used by seed companies to measure the presence or absence of specific DNA sequences or the expression of proteins encoded by that DNA.

By and large, two tests are used to detect GE content (Bonfini et al., 2002; Miraglia et al., 2004). One is polymerase chain reaction (PCR)-based testing, in which a fluorescent signal can be used to verify and quantify the amplified DNA used. PCR testing has the advantage of being fast and relatively simple. Primers can be developed for specific DNA sequences. At the least specific level, promoters or terminator sequences may be used for screening. More advanced is testing that involves probes made to the specific gene that has been used to transform a plant, such as a *Bt* gene; however, caution must be exercised when using these gene sequences for testing if they are naturally occurring genes because false positives could be obtained. The third level of specificity for detecting GE content involves the use of construct-specific sequences that are derived from the junction between two DNA elements, for example, a promoter and a target gene. These junctions are probably not found naturally and offer a uniqueness that adds to test specificity, although different GE traits may share promoter-target gene combinations. The highest level of specificity is attained when probes are developed for the unique junction found at the integration locus between the inserted DNA and the recipient genome. These event-specific sequences generally offer the best targets for probe development and eventual test specificity.

The other test is enzyme-linked immunosorbent assay (ELISA), which tests for the protein product of a functional or modified gene. ELISA, or antibody-based testing, has been routinely used to measure novel-protein expression. It has the advantage of measuring gene products, but it may not always be available for all commercialized GE traits. Results can be variable, depending on antibody specificity and the other constituents of the food matrix that may interfere with testing.[a] It is important to note that antibody tests for processed food products may be ineffective because processing, whether by heat or by other means, can cause conformation changes in a protein that can reduce antibody specificity for the

approved for import in all major markets. If an importing country does not start its regulatory review process until the new crop has first been approved in the producing country, the delay from first regulatory approval to commercialization is at least 2–3 years (Fraley, 2014). Some developers of new GE crops have introduced their products with plans to ensure a separate distribution channel for the crops from conventionally bred varieties until export market approval has been received (Richael, 2015). Growers associations may also work with farmers producing for export markets to protein. In contrast, ELISA tests can be engineered for field-level use that enables assays in production fields and other locations along the supply or distribution chain.

A number of other tests can be used to detect GE content. They include microarrays that can be used to detect multiple events, Surface Plasmon Resonance, mass spectrometry, and near-infrared spectroscopy. Bioassays can be used for herbicide-resistant (HR) crops. These are basically germination tests, whereby HR varieties are distinguished from their non-HR counterparts because the HR varieties will germinate and grow in the presence of the paired herbicide. Bioassays have the advantage of being relatively easy to perform and less expensive, but they take up to a week to complete (Thomison and Loux, 2001).

As with any testing program, it is important to understand not only the measurement or test being used (that is, its sensitivity and selectivity) but the sampling program and the preparation of the sample. Testing programs can be organized differently depending on the objective. For example, if GE content is being tested in a sample of a bulk commodity grain, it is likely that the GE content is not homogeneous within the raw product. A sampling strategy would need to take that factor into account. Lot size, uniformity, and tolerance are key attributes of the sample that need to be considered in developing the sampling scheme. A number of sampling strategies have been developing for testing bulk raw products. Many of them are adaptations of schemes developed to detect such food contaminants as mycotoxins, but some have been designed specifically for detecting GE content (for example, programs in USDA's Grain Inspection, Packers and Stockyards Administration). Such initiatives as the Non-GMO Project have also developed standards and guidance on sampling strategies and requirements for testing.[b] The project's standard is designed to certify products as "GMO-free" and describes the importance of statistically valid sampling plans that are based on risk-assessment plans and the need to use testing laboratories that are ISO 17025 accredited. A number of food companies use third-party testing companies or perform internal testing to verify the status of their products.

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[a] GMO Testing: Strip Test (Lateral Flow Device). Available at http://www.gmotesting.com/Testing-Options/Immuno-analysis/Strip-Test. Accessed November 6, 2015.

[b] Non-GMO Project Standard. Available at http://www.nongmoproject.org/product-verification/non-gmo-project-standard/. Accessed November 6, 2015.

ensure that they are aware of the regulatory status of GE crops in other countries before they select varieties for the next planting season.[21]

An important consideration is that the tolerance that a country sets for the presence of unapproved GE traits has substantial economic implications. The lower the tolerance, the more expensive the efforts to test and

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[21] For example, see the National Corn Growers Association's *Know Before You Grow*. Available at http://www.ncga.com/for-farmers/know-before-you-grow. Accessed November 6, 2015.

segregate products throughout the food production and distribution chain. The issue is complicated by the fact that testing equipment can now detect GE content at very low levels; this may encourage national governments to reduce their tolerances. However, achieving complete segregation is not possible. Indeed, a 2010 National Research Council report on sustainability found that "zero tolerance for the presence of GE traits in non-GE crops is generally impossible to manage and is not technically or economically feasible" (NRC, 2010b:171). That report was presumably referring to the GE varieties of bulk commodity crops on the market in 2015 rather than to specialty crops, such as papaya, but there is an unresolved tension between importing countries, which often set tolerances based on the degree of product purity that can be tested, and exporting countries, which are constrained by the degree of product purity that can be achieved.

Stein and Rodríguez-Cerezo (2009) and Parisi et al. (2016) posited that problems posed by asynchronous approval are likely to worsen as more traits are introduced into a wider variety of crops and as the gaps between regulatory approvals grow. The committee agrees that this is likely and that trade disruptions related to crops with GE traits—whether because of asynchronous approvals or violations of tolerance thresholds—are likely to continue to occur and to be expensive for exporting and importing countries.

> **FINDING: Trade disruptions related to crops with GE traits due to asynchronous approvals and violations of tolerance thresholds are likely to continue to occur and to be expensive for exporting and importing countries.**

Effects of Regulation on the Development and Introduction of New Genetically Engineered Crops

The development and introduction of new GE crops are affected by regulatory-approval processes. In the case of GE food and crops, as with other products, the purpose of any regulatory product-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 (as defined by the relevant regulatory or legal standard). In effect, regulations operate as a bar to market entry of products that do not meet legal requirements for safety and efficacy. Regulations also provide a social and market benefit by helping to ensure consumer confidence in the safety and efficacy of new products (Stirling, 2008; Millstone et al., 2015).

Regulatory-approval systems also impose a variety of costs. Regulations impose direct costs on product developers to compile the data required to complete regulatory review. The time, delay, and uncertainty associated with regulatory review and approval before a product can be marketed also constitute an indirect cost for product developers.

In addition to increased costs for product developers, regulations can create broader social costs. To the extent that a new product provides agronomic, economic, or other benefits, such as those for GE crops discussed elsewhere in the chapter, any delay in bringing the product to market associated with the regulatory review process defers the benefits and thus imposes indirect costs on those who would otherwise have enjoyed the benefits of the new product. Furthermore, regulatory processes are by nature knowledge-learning processes, and the possibility exists that regulators will make mistakes, such as type I errors which entail approving unsafe or ineffective technologies and type II errors which entail rejecting beneficial technologies (Carpenter and Ting, 2005, 2007; Hennessy and Moschini, 2006; Ansink and Wesseler, 2009).[22] Either type of error imposes unnecessary societal costs. Quantifying and comparing direct and indirect costs and benefits are notoriously difficult. As discussed elsewhere in the chapter, benefits associated with adopting GE crops may be estimated by ex ante or ex post studies but with substantial caveats and uncertainties. Similarly, estimating the benefits of regulation (including harm avoided) is at least equally challenging. The benefits of harm avoided is evident in some of high-profile cases already mentioned in Chapter 5 and earlier in this chapter's section "Constraints on Trade." Aventis CropScience, the maker of StarLink™ maize, paid over $120 million to settle various lawsuits (Cowan, 2013; see "Food Allergenicity Testing and Prediction" section in Chapter 5). Journalists have estimated the total economic damage at nearly $1 billion (Lueck et al., 2000). The cost of LibertyLink rice to the European rice industry has been estimated at €50–110 million, which is equivalent to 27–57 percent of the total market's gross margin (Stein and Rodríguez-Cerezo, 2009). Furthermore, weak regulatory oversight led to the overuse of glyphosate in maize, cotton, and soybean crop production, which has been credited with the emergence of glyphosate-resistant weeds (Livingston et al., 2015). One USDA study found that maize growers with glyphosate-resistant weeds lost $148–165/hectare compared with maize growers who did not face glyphosate-resistant weeds (Livingston et al., 2015). Glyphosate resistance might have been delayed if regulators had followed the advice of some weed scientists who foresaw the problem and made recommendations (Mortensen et al., 2012).

An important issue is that estimates of regulatory costs do not capture less easily monetized issues. For example, it is difficult to measure the cost to farmers and society of losing the herbicide glyphosate because it is con-

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[22] Although all references describe models that incorporate regulatory errors in decision-making, the committee was not aware of any studies that apply these approaches explicitly to GE crops.

sidered more benign than many of the chemicals that it replaces (Mortensen et al., 2012). It is similarly difficult to capture the cost of a loss of public trust in a product, an industry, or the legitimacy of a regulatory system (Stirling, 2008; Millstone et al., 2015).

As discussed in Chapter 9, regulatory systems vary in their approaches to balancing potential costs and benefits. Regulatory systems that are more precautionary and weighted toward preventing type I errors can impose relatively higher costs and uncertainty for producers to complete regulatory review.[23] Whether any one particular regulatory approach does better than another in terms of achieving optimal net social welfare through balancing costs (such as innovation lag) and benefits (such as harm avoided) is a topic well beyond the scope of this report. Furthermore, the tradeoffs of benefits and costs involve policy value choices likely to differ among societies and stakeholders (see Chapters 5 and 9).

One of the predominant concerns raised about the costs associated with regulatory approval of new GE crops and foods is that they may operate as a barrier to innovation in GE crops (Kalaitzandonakes et al., 2007; Bayer et al., 2010; Graff et al., 2010; Phillips McDougall, 2011). The costs of obtaining regulatory product approval for new GE products may operate as a barrier to entry particularly for public-sector and small private firms (Falck-Zepeda et al., 2012; Smyth et al., 2014c). Jefferson et al. (2015) and Graff and Zilberman (2016) have argued that regulations can be "excessively strict" and result in unnecessary barriers.

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[23] A "real-options model" has been used in several studies to estimate the effect of a decision-making model that compares a precautionary approach that favors delaying a regulatory approval pending additional information with a decision-making model that favors making an immediate decision with existing information (Beckmann et al., 2006; Wesseler et al., 2007; Wesseler, 2009). Kikulwe et al. (2008) used the real-options model to examine the potential adoption in Uganda of banana with genetically engineered resistance to black sigatoka fungus. Their estimations considered reversible and irreversible costs and benefits and showed that the opportunity cost for regulatory delays implies forgoing benefits of $179–365 million per year. Furthermore, the authors estimated that if social irreversible benefits of about $303/hectare are considered, farmers who adopted the GE banana would not be willing to pay more than $200/hectare for transaction, R&D, and regulatory costs. When area planted with bananas in the country was taken into consideration, the results implied that the total cost of development, including regulatory costs and technology transfer, cannot be higher than $108 million for Ugandan farmers to adopt the GE banana.

Demont et al. (2004) and Wesseler et al. (2007) used the real-options model to examine the effects of the potential introduction of HR sugar beet and *Bt* and HR maize into the EU for cultivation. Their results indicated that there may be good economic reasons and incentives for producers to adopt and use the technology as measured by the aggregation of income accruing to farmers. However, estimated effects on a country's income are expressed on a per capita basis and estimated favorable income effects are quite small; thus, it may be reasonable to postpone the decision of whether to approve both crops in the EU. In other words, estimated benefits accrued to a small number of producers and there was no effect in the welfare of all citizens.

The published literature, however, provides only an incomplete understanding of the marginal direct and indirect costs associated with the regulatory-approval process for GE crops that would be needed to assess the effects of regulatory costs on innovation and market entry. Understanding the effects of regulatory costs requires, for example, the exclusion of costs of research and product development that would be necessary to get a product to market even in the absence of a regulatory-approval process. Typically, however, firms zealously guard product-development estimates because they may provide a competitive advantage to competitors in tight and often imperfectly competitive markets (Kalaitzandonakes et al., 2007). The published studies of the cost of regulatory approval have not used a consistent methodology, and it is not always clear what costs are included and how they have been estimated. Cost estimates in the literature vary substantially and can be influenced by many factors, including overhead and management costs and costs of basic early discovery and R&D.

One study estimated that it costs private-sector firms about $35.1 million to achieve regulatory compliance, which encompasses approval of the commercial cultivation of a GE crop in at least two countries and import approval of the crop for food and feed purposes in at least five markets (Phillips McDougall, 2011). Relying on a Monsanto document, Graff et al. (2010) estimated that costs of commercializing a single trait range from $50 to $100 million and that about 70 percent of that goes for the development stage in which regulatory compliance is secured. Estimates by Kalaitzandonakes et al. (2007) were much lower: They calculated that the range of direct compliance costs of obtaining regulatory approval of a private-sector–developed GE event in 10 markets (Argentina, Australia, Canada, China, the EU, Japan, Korea, the Philippines, Taiwan and the United States) was $7.1–14.4 million for IR maize and $6.2–14.5 million for HR maize.

The committee heard directly from large and small companies about the cost of regulation. Representatives of Bayer CropScience, Dow AgroSciences, Dupont Pioneer, and Monsanto made presentations to the committee at its public meeting in December 2014. The representatives of Dupont Pioneer and Dow AgroSciences cited the estimated cost of regulatory compliance in the Phillips McDougall (2011) study (Endicott, 2014; Webb, 2014). The Dupont Pioneer representative noted that the development of a GE variety was similar to the development of a conventionally bred hybrid variety but that it typically takes 13 years to bring a GE variety to the market (versus 7 years for a conventionally bred hybrid) because of the regulatory requirements (Endicott, 2014). The reason for that difference is that, although compositional analyses are often performed on new varieties to demonstrate that they are within normal genetic variation, toxicity tests and environmental assessments that are not performed on conventionally bred crops are performed on GE crops (Fraley, 2014). The Monsanto representative stated that the regulatory costs are manageable for large-area crops such as maize but are problematic for small-area crops (Fraley, 2014). The representative of Bayer CropScience posited that unnecessary data requirements and lack of harmony in regulatory systems among countries make regulatory frameworks too expensive for developing countries to operate, and this discourages them from adopting available GE crops (Shillito, 2014a). The lack of regulatory harmony on the international scale also curtails dissemination of new GE varieties because companies cannot afford the costs of registering the same GE variety multiple times for different markets. Some developers have opted to limit the distribution of their products to a country or a region to minimize expenses of complying with varied regulatory requirements in different countries (Shillito, 2014b).

The committee heard from representatives of smaller companies in a number of webinars. A representative of Forage Genetics International, which has developed GE varieties of alfalfa, estimated that it cost $50–75 million to commercialize a new GE variety. That estimate included trait development, product development, and regulatory approvals in the countries where the alfalfa would be grown or where harvested alfalfa would be sold; roughly half the costs could be attributed to meeting regulatory requirements in countries growing or buying GE alfalfa (McCaslin, 2015). A Simplot Plant Sciences representative estimated that the cost of getting the company's first nonbrowning potato variety through the U.S. regulatory system was $15 million (Richael, 2015); this estimate was for regulatory costs alone and did not include varietal development costs. The cost was presumably higher for its second nonbrowning potato variety which, unlike the first variety, included a plant-incorporated protectant that provides resistance to the late blight fungus (Richael, 2015). The estimate also did not include costs associated with regulatory approval in export markets. The president of Okanagan Specialty Fruit, an eight-person company that developed the nonbrowning apple, suggested that the out-of-pocket regulatory costs of the company's first approved product were much lower, around $50,000. However, the long timeframe to gather the field data for the submission to the U.S. and Canadian regulatory agencies (5–6 years) and to respond to and wait for responses from the regulatory agencies before regulatory approval (5 years for the United States, over 3 years for Canada) entailed a substantial cost in staff salaries during a time in which the company had no commercial product. Total costs were estimated to be about $5 million (Carter, 2015; N. Carter, Okanagan Specialty Fruit, personal communication, January 12, 2016). Unlike Forage Genetics International and Simplot Plant Sciences, Okanagan Specialty Fruit did not pursue regulatory clearance from other markets because there were no plans to export.

The committee also heard from a government scientist and a university researcher who developed GE fruit trees and took them through the U.S. regulatory process. Researchers at Cornell University and the University of Hawaii cleared the U.S. regulatory process for the VR papaya in 1998 (Gonsalves, 2014). Regulatory compliance was also sought in Japan because it is a large export market for U.S. papaya. The process started in 1999 and was finished in 2011; part of the reason that it took so long was that the U.S. scientists did not have the time or funding to devote full-time attention to navigating the regulatory process (Gonsalves, 2014). Scientists at USDA's Agricultural Research Service began the regulatory-compliance process in 2003 for a GE plum variety with resistance to plum pox virus; the process was completed in 2011 (Scorza, 2014). The VR papaya was the only commercialized GE crop grown in the United States in 2015 that was developed through the public sector. The president of the Two Blades Foundation, a research organization that supports the development and deployment of durable disease resistance in crops, told the committee that many GE traits for disease resistance have been demonstrated by university scientists but that the existing regulatory-compliance costs are prohibitive for these researchers or their institutions to turn a proof-of-concept study into a commercial product (Horvath, 2015).

Costs of regulatory compliance are considered even more constraining for developing countries, in which a small firm or public research organization may consider compliance too expensive and the uncertainty too great (Bayer et al., 2010). Estimates of direct regulatory costs for four GE crop events (*Bt* eggplant, VR tomato, *Bt* rice, and VR papaya) being advanced by public institutions in the Philippines when the Bayer et al. study was conducted in 2007–2009 were reported to range from \$249,500 to \$690,680. Those costs are substantially lower than the \$2.6 million estimated by Manalo and Ramon (2007) for the technical and commercial development of Monsanto's IR maize event, MON810, in the Philippines. Cost discrepancies in the Philippines studies can be attributed partially to the fact that the direct costs for the four public-sector events were for a small number of activities taking place in the Philippines and excluded R&D, technology transfer, and compliance testing for the events or their novel proteins that took place outside the Philippines or had already been completed for like products. The cost of MON810 commercialization in the Philippines reflects the studies and activities conducted from the gene-discovery phase to the first set of laboratory and greenhouse experiments in the United States, as well as costs incurred in the Philippines. Furthermore, if the approval were to scale beyond the Philippines to the standard discussed above (approval of cultivation in two countries and import approval in at least five markets), the estimate for regulatory compliance would be about \$55 million (Pray et al., 2006).

Cost estimates in some of the published studies, particularly in the developing countries where regulatory frameworks are still in development, are more of the ex ante type; hence, costs are derived from "best-guess" estimates. In the after-the-fact studies, the approach simply followed the collection of data on costs of complying with regulation. The estimates do not include social costs, such as government-sector regulatory costs, social-welfare losses, or transitional and indirect costs (Falck-Zepeda, 2006), nor do the studies reflect opportunity costs of capital that potentially could be invested elsewhere, as is done in the pharmaceutical industry (DiMasi et al., 2003).

The results available in the literature showcase the need to use robust, consistent, and rigorous methods to estimate the cost of regulations and the effects of regulation on innovation. The methods chosen will need to be flexible enough to accommodate a changing regulatory environment that may affect activities performed to demonstrate safety or to obtain regulatory approval by the appropriate regulatory agency and to promote cost efficiency within the system, especially in developing countries. There is also a need to acknowledge that regulations refer to more than biosafety 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. Such concepts as *responsible innovation* refer to efforts to move beyond expert-driven biosafety assessments and to implement inclusive and deliberative approaches to assess and distribute risks and benefits (Macnaghten and Carro-Ripalda, 2015). Such governance issues are discussed in more detail in Chapter 9.

FINDING: Regulation of GE crops inherently involves tradeoffs. It is necessary for biosafety and consumer confidence, but it also has economic and social costs that can slow innovation and deployment of beneficial products.

FINDING: Estimates of the regulatory costs of GE crop development vary widely by study and by trait-crop combination.

RECOMMENDATION: A robust, consistent, and rigorous methodology should be developed to estimate the costs associated with taking a GE crop through the regulatory-approval process.

Intellectual Property

The outputs of research can exist as private goods or as public goods. A private good must be purchased to be used, and its use by one person makes it unusable by another person; thus, private goods are excludable and rivalrous. A public good is available to people without payment, and its use by one person does not make it unusable by others; thus, public goods are nonexcludable and nonrivalrous. Public goods are traditionally associated with the public sector (universities and government laboratories) and private goods with the private sector (industry), although this distinction is becoming less obvious. GE crops research outputs can exist as private or public goods, depending on what kind of intellectual-property restrictions developers use to limit access to the outputs.

For much of the history of agricultural crop research and improvement, crop seeds have been treated as having characteristics consistent with public goods. Farmers regularly saved a portion of their harvest as seed to be planted in the next year (Kloppenburg, 2004). Seeds from open-pollinated and self-pollinated crops under those circumstances were nonexcludable in that the farmers did not pay for them and nonrivalrous in that seeds could be propagated, replanted, and exchanged. Therefore, as Halewood (2013:285) noted, “For millennia, very little (or no) human effort was expended to exclude access to plant genetic resources for food and agriculture.” Until the 20th century, seeds were considered public goods (Halewood, 2013). However, beginning in the early 20th century, some crop seeds started to transition to private goods with changes in the ability of developers to limit access through intellectual property and other instruments. In the United States, that shift occurred through a number of biological, legislative, and judicial changes and culminated in the potential to patent all plants (Box 6-7).

Intellectual-property regimes, especially patents, play a substantial role in shaping the kinds of products available (and often therefore the planting decisions available) to farmers. Patent law, seed-market concentration, and public-research investment can have various social and economic effects. Because of the large contributions that U.S. companies and U.S. universities make to research in crop improvement, much of the discussion and literature focuses on the intellectual-property regime of the United States.

Patent Law

There are benefits of a strong intellectual-property regime, especially patents. First, patents make an innovation publicly known through publication, as opposed to trade secrets, which limit information exchange (Dhar and Foltz, 2007). Second, by providing protection to an inventor, patents create an incentive to invest in R&D in that there is a chance to secure a return on the initial investment. Third, patents can facilitate the assigning of risks and responsibilities for an invention in the cases of unintended consequences. In the specific cases of agricultural crop R&D, the applica-

BOX 6-7
Transition of Agricultural Crop Genetics from Public to Private Goods

Before the introduction of hybrid plants, seeds were public goods in that they were largely nonexcludable and nonrivalrous (Halewood, 2013). Farmers could plant seed saved from an earlier season, with no cost for the seed and with reliably consistent yields, and one farmer's saving seed did not prevent another from doing so. Hybrid varieties represented a first step from seed as public good to seed as private good because seed saved from a hybrid crop's harvest does not yield nearly as well as the hybrid parent.[a] Farmers who wanted to grow hybrid varieties, which had greater yields than the nonhybrid varieties that farmers had been saving and replanting, had to buy new seed from the hybrid seed provider each season. Some row crops, such as maize and cotton, were amenable to hybridization, but other row crops, such as soybean and wheat, were less amenable and therefore remained in the sphere of public goods.

Not all crops, however, are produced from seed. Perennial crops, such as apples, lemons, grapes, and strawberries, are as nonexcludable and nonrivalrous as seeded crops and are usually reproduced asexually by planting a cutting of an original plant or by grafting a cutting from one plant on to another. The 1930 Plant Patent Act in the United States allowed plant breeders an option to shift those asexually reproduced types of crops from public goods to private goods by applying for a specialized patent to prevent the copying of protected plants through such practices as propagation of cuttings or by tissue culture (Huffman and Evenson, 2006).[b]

The 1970 Plant Variety Protection Act (PVPA), which was in line with international trends of the International Union for the Protection of New Varieties of Plants (UPOV) Convention adopted in Paris in 1961, created in the United States something similar to a plant patent on sexually reproduced crops, such as wheat and soybean. However, under the PVPA, farmers are allowed to save seed for their own use (but not to sell the seed), and public-sector scientists are allowed to conduct research and develop innovations using patent-protected varieties.

With the 1980 Bayh-Dole Act and the 1980 Stevenson-Wydler Act, the U.S. government allowed for the privatization of outputs from federally funded research and encouraged private–public research collaborations (Fuglie and Toole, 2014). Following the United States' lead, many Organisation for Economic Co-operation and Development countries established similar policies (Gering and Schmoch,

tion of patent protection to GE crops means that firms can secure a return on their research investments in GE seeds and thus have an incentive to apply their resources to more agricultural crop research and innovation (Fuglie et al., 2012).

Despite those benefits, a number of concerns have been expressed about the application of the patent system in the United States. A National Research Council report from 2004 on how to update the U.S. patent sys-

2003). Also in 1980, the U.S. Supreme Court decided in *Diamond v. Chakrabarty* that living organisms that were invented, modified, or engineered could be patented.[c] However, it was not until 1985 that the U.S. Patent Office Board of Patent Appeals decided in *Ex Parte Hibberd* that utility patents could be extended to all plants (Van Brunt, 1985).

Although the 1985 *Hibberd* case applied to plants, there was an ongoing contestation over the validity of utility patents on non-GE crops until 2001 when the U.S. Supreme Court in *J.E.M. Ag Supply v. Pioneer Hi-Bred* endorsed the application of utility patents to newly invented or developed GE and non-GE crop varieties, in addition to the application of PVPA (Janis and Kesan, 2002; Sease, 2007). Utility patents apply to the invention or discovery "of any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof" (USPTO, 2014).

The application of utility patents to all types of new crop varieties in the United States created the possibility for all plants that met the criteria of utility patents to be protected as private goods for up to 20 years. Unlike plant-variety protection, utility patents can be used to restrict the freedom to operate of public-sector researchers and farmers (Huffman and Evenson, 2006). Before 2001, hundreds of utility patents had been granted to non-GE crops in the United States (Janis and Kesan, 2002). As of 2007, some 2,600 patents had been granted to non-GE crops in the United States (GRAIN, 2007). They included crops, like wheat, that had previously remained public goods because no GE varieties or hybrid varieties were available. Although many crop varieties are still public goods, results of future research on crops that are publicly available could be patented. Le Buanec and Ricroch (2014:69) stated that, given the different levels of protection between PVPA and a utility patent, "it is not surprising that in the USA breeders are massively applying for patent protection for their varieties." As Busch et al. (1991:28) argued, genetic-engineering technologies have been a key vector in the progressive privatization of crop germplasm because, in part, genetic-engineering technologies "challenge the belief that plants are merely the products of nature."

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[a] Hybrid maize was first sold in the United States in 1910s.

[b] The 1930 Plant Patent Act did not apply to tuber crops such as potato.

[c] In *Diamond v. Chakrabarty*, General Electric had filed a patent for a bacterium genetically engineered to break down crude oil. The patent application had been rejected because living organisms were not thought to be subject to patents under existing U.S. law.

tem for the 21st century concluded that high rates of innovation indicated that the patent system should not be changed in any fundamental way. However, the report also highlighted legal and economic changes over the last few decades that were "putting new strains on the system" (NRC, 2004:1). The report was about the U.S. patent system in general and not specific to innovation in agricultural crops, but some of the strains noted are relevant to challenges and concerns associated with the application of utility patents to plants, including GE crops. The report found that the volume of patenting activity had increased and that patent-holder rights had been strengthened in the United States and internationally. It also observed that some firms were engaging in strategic patenting to gain access to others' technologies and to avoid future infringement litigation[24] and that the costs of the patent system were increasing. Of specific relevance to agricultural crops, the report concluded that new fields of research (such as living organisms) had become patentable, but their effects on patent law had not been systematically studied. Furthermore, the report conceded that it was possible that patents on foundational discoveries and research tools might impede scientific progress. The report asserted that the right policies are needed to promote synergy among the U.S. patent system, innovation, and economic growth.

The findings of the 2004 National Research Council report need to be examined in relation to the application of patents to GE crops as well as conventionally bred crops. A growing body of work questions whether patents are conducive to innovation in agriculture. The claim is that patents limit farmer and crop-researcher experimentation and development (Kloppenburg, 2010). Since the mid-1990s, a broad array of biotechnology researchers have recognized the need to "examine the effects of intellectual property protection on the development, dissemination, and utilization of research tools" (NRC, 1997:viii). In the biomedical field, the National Institutes of Health (NIH) recognized that the goal of commercialization could conflict with the broad dissemination of research findings and research tools and established a policy for its grant recipients to promote the sharing of findings and tools (NIH, 1999). After NIH's policy change, the U.S. Congress amended the 1980 Bayh-Dole Act in 2000 to include this statement: "'It is the policy and objective of the congress to use the patent system to promote the utilization of inventions arising from federally supported research and development . . . to ensure that inventions made by nonprofit organizations and small-business firms are used in a manner to promote free competition and enterprise *without unduly encumbering future research and discovery*'" (emphasis added by Reichman et al., 2010:3). However, a policy similar to that of NIH has not yet been implemented in the United States for agricultural research.

An effort has been made to use biological open-source arrangements to establish a protected plant genetic-resource commons (Jefferson, 2006;

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[24] Cahoy and Glenna (2008) have described the problem of patent thickets in bringing a new agricultural crop to market. The United States tends to allow a private ordering to overcome the patent thickets, which generally occurs when a large company purchases or makes a strategic alliance with a smaller company to secure the smaller company's patents. Private ordering may be an efficient strategy for sorting out thickets, but it has adverse outcomes, the most prominent being greater economic concentration (see section "Seed-Market Concentration" below).

Kloppenburg, 2010). Protecting the commons means that genetic resources are not treated as part of the public domain because that would make crop improvements vulnerable to private appropriation. Rather, protecting the commons is a strategy for creating intellectual-property protection so that the commons cannot be appropriated (Kloppenburg, 2010).

That effort has led to the creation of the Open Source Seed Initiative (OSSI) at the University of Wisconsin, an organization dedicated to bringing together farmers, breeders, and small seed companies to share plant genetic resources. Another organization with a similar mission is CAMBIA-BiOS (Biological Innovation for Open Society). Founders of those organizations have acknowledged that there are substantial differences between computer software (the basis for the open-source model) and agricultural germplasm (Jefferson, 2006; Kloppenburg, 2010). Halewood (2013:292) observed that the costs of software creation are "trivial compared to those associated with globally dispersed costs and time associated with the generation, maintenance and sharing of" plant genetic resources for food and agriculture. However, Jefferson (2006) and Kloppenburg (2010) both emphasized that OSSI and CAMBIA-BiOS are building on the open-source computer-software model to promote their organizational missions.

There is good reason to draw comparisons with the software model. Pearce (2012) noted that open-source software is outperforming the intellectual-property–protected software generated by the Microsoft Corporation, one of the largest and most powerful private companies in history. Furthermore, Pearce reported that many existing technologies could solve numerous problems and save millions of lives if intellectual-property protections were not limiting access. Giving smallholder farmers in developing countries greater control over their seeds, with other forms of agricultural knowledge and technology, may be foundational to promoting their social welfare (Kloppenburg, 2010; Wittman, 2011).

Some have argued that patents on GE crops should be regulated under the 1970 Plant Variety Protection Act or the 1978 Convention of the International Union for the Protection of New Varieties of Plants (Ervin et al., 2000). Such a policy change would enable university scientists to conduct research without concern about patent infringement; that would be in line with a suggestion made by the 2004 National Research Council report to shield university researchers from liability related to the noncommercial use of patent inventions (NRC, 2004). In addition to promoting crop innovations, such a policy change might increase biodiversity (Hubbell and Welsh, 1998; Ervin et al., 2000) and would allow farmers to save, replant, and crossbreed patent-protected crops legally.

In 2015, the legal constraints were such that when a crop invention—GE or non-GE—was patented, users had to pay a licensing fee or otherwise gain permission for the right to plant it and to conduct research on it.

Reactions to those constraints have played out in complex ways around the globe, with crops like *Bt* cotton in India and HR soybean in Brazil. In both cases, farmers saw advantages to using what Herring (2016) referred as "stealth seeds." National governments and private companies have sought to control the spread of stealth seeds because of the potential biosafety risks and the lost licensing revenue for the patented seeds (Herring, 2016).

The implication of those legal constraints for university and government researchers has been that they must secure material-transfer agreements to gain access to patented materials for research purposes; this has been cited as a potential obstacle to innovation (Wright, 2007; Lei et al., 2009; Glenna et al., 2015). Some academic researchers contend that patenting GE crops facilitates university–industry knowledge-sharing, innovation, and the commercialization of useful goods; that the outcomes enhance social welfare; and that barriers to university–industry collaborations should be overcome (Etzkowitz, 2001; Bruneel et al., 2010). However, some studies indicate that intellectual-property protections may be hindering research and innovation (Lei et al., 2009) in that a firm or university holding a patent on plant germplasm may legally block research on the crop. The Public Intellectual Property Resource for Agriculture, a clearinghouse for intellectual-property information in agricultural biotechnology, was developed to address some of the concerns raised by patents on GE crops, such as patent thickets and constraints on research (Graff and Zilberman, 2001). However, university scientists report that patent protections limit their ability to publish research findings, constrain university research freedom, inhibit research that might be useful in evaluating the efficacy and environmental effects of a GE crop, and, in the long term, may reduce innovation (Wright, 2007; Waltz, 2009; Glenna et al., 2015). As discussed above, the 2004 National Research Council report on the U.S. patent system recommended that there be "some level of protection for noncommercial uses of patented inventions" (NRC, 2004:82).

Results from studies on the overall effects of intellectual-property protections on crops are mixed. In 2005, the International Seed Federation commissioned a study of the revenue lost to farmers saving seed (Le Buanec, 2005). It is generally recognized that most farmers in developing countries rely on seed-saving, but seed-saving is also common in developed countries. After surveying 18 countries to determine the extent of farmers' saving seed of improved crops, the author concluded that each year seed firms lost nearly $7 billion and the average plant-breeder royalty losses were just over $472 million (Le Buanec, 2005). From farmers' perspective, that is about $7 billion that they do not need to pay for seeds each year. For private seed firms, that is lost revenue and a disincentive to invest in seed R&D. There are broad policy questions about getting the balance right to promote innovation in the seed sector while recognizing the tight margins that farmers face.

However, in the specific case of intellectual-property protection on private investments, there is robust evidence in developed and developing countries that the effects have been positive (Fernandez-Cornejo, 2004; Eaton et al., 2006; Pray and Nagarajan, 2009). In a study in India, Kolady et al. (2012) examined the effect of improving seed policies that incorporated intellectual-property protection on private investments and on yields of selected crops. In the study, hybrid crops (maize and pearl millet) had enhanced intellectual-property protection under the improved seed policy regime, whereas self-pollinated crops (rice and wheat) did not. The study found a statically significant effect on yields of hybrid crops after changes in the seed-policy regimes that included intellectual-property protection but no effect on yields of self-pollinated crops. The study provided evidence that policy reforms without some intellectual-property protection are insufficient to enhance private investments in the seed sector. Results from the Kolady et al. (2012) study were similar to those on the effect of the Plant Variety Protection Act on yields of selected crops in the United States (Naseem et al., 2005; Kolady and Lesser, 2009).

A separate concern about the patent system as it is applied to GE crops is related to the responsibilities for a patent holder and for those who purchase the right to use the patent. Some research has indicated that judicial decisions in the United States and Canada have led to the "technology developers gaining some of the most important benefits of ownership while remaining exempt from its liabilities" (Pechlaner, 2012:13). On the one hand, farmers' rights to ownership of the GE crop seeds that they purchase are limited to planting the seeds and selling the grain. They cannot save the seed. Because the GE trait cannot be separated from the germplasm, the company effectively owns the germplasm. On the other hand, farmers in the United States and Canada are held responsible for gene flow if they plant seeds that they know were fertilized by GE pollen from a neighboring farm. That creates a double standard in that the firm maintains ownership of the gene when the farmer wants to replant it, but the firm does not bear responsibility for any damage caused by the gene when it blows into a neighbor's field. If the patent rights were applied consistently, the firm would own the gene and be responsible for the damages from gene flow or the farmer would own the plant and be responsible for the damages (Kinchy, 2012; Pechlaner, 2012).

Finally, intellectual-property regimes need to be appropriately applied and checks and balances are needed to ensure that patents and other intellectual-property protection instruments do not overstep intended boundaries or objectives, which could cause unnecessary legal disputes. The case of the yellow bean (*Phaseolus vulgaris*) is a cautionary tale about the inappropriate application of utility patents to crops, in this case to a conventionally bred variety. Two varieties of traditional yellow beans were developed independently in Peru and Mexico. Mexican bean breeders eventually crossed the two varieties to create a new yellow bean, and many Mexicans adopted yellow beans into their diets. In the 1990s, a firm in the United States obtained yellow bean seeds, planted them for 3 years, and then applied for a patent on the bean, claiming that the color was novel. The U.S. Patent and Trademark Office awarded the patent, so farmers and marketers who were growing and selling the yellow bean in the United States were now infringing on a patent. Patents are only valid in the issuing country, however, so someone from Latin America who tried to export yellow beans to the United States could find himself or herself infringing on a patent. The patent was later revoked because scientists at the University of California, Davis used DNA fingerprinting technology to demonstrate that the yellow bean was not novel (Pallotini et al., 2004). That case has at least two implications: Molecular-genetic research techniques can be useful in disqualifying patents on conventionally bred crops, and the granting of utility patents on crops has favorable and unfavorable social effects. Whether a patent is applied to conventionally bred or GE crops, 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 patent on the yellow bean was thrown out because a group of researchers at a land-grant university took an interest in the case, but not all farmers, breeders, and seed and grain marketers have the resources to challenge such inappropriately issued patents.

Seed-Market Concentration

Another concern related to utility or plant patents for GE crops is their potential contribution to the concentration of the seed market. Concentration is a concern because the purported benefits of a competitive market, such as fair prices, are likely to be diminished (Glenna and Cahoy, 2009). Market concentration can be documented in at least three ways. First, one can look at the change in the market share of the largest firms in an industry. Fuglie and Toole (2014) used the four-firm concentration ratio. According to that measure, when four or fewer firms control more than 40 percent of a market, a market is considered to be potentially concentrated (Breimyer, 1965; Connor et al., 1985). Fuglie and Toole found that globally four firms controlled 21.1 percent of the seed-market share in 1994, 32.5 percent in 2000, and 53.9 percent in 2009. Such growth indicates a steady increase in market concentration may be correlated roughly to the period of the introduction and widespread adoption of GE crops (also see Fernandez-Cornejo and Just, 2007; Howard, 2009).[25] Whether the introduction of GE crops increased the speed at which the seed sector became more concentrated is still debatable.

A second way to document market concentration is to show how a small number of large companies have gained control of the intellectual property associated with GE crops. Since GE crop research began in the 1980s, 37 companies have secured patents on GE maize and 118 companies have secured patents on non-maize GE crops. However, through buyouts and strategic alliances, just three companies controlled 85 percent of patents on GE maize in 2008, and three companies controlled 70 percent of patents on non-maize GE crops (Glenna and Cahoy, 2009). That constitutes substantial concentration.

A third way is the Herfindahl-Hirschman Index (HHI), which is an indicator that the U.S. Department of Justice (DOJ) uses to measure market concentration. The HHI is used to determine the average market share of firms in an industry. The HHI is calculated by summing the squared market shares (expressed as fractions or whole percentages) for all firms in an industry. DOJ defines a market as being moderately concentrated when it reaches an HHI score of 1,000; a score above 1,800 indicates high concentration. Fuglie and Toole found that the HHI for the global crop-seed sector was 171 in 1994, 349 in 2000, and 991 in 2009. However, their calculations included the entire seed sector and the entire world, as opposed to only maize, soybean, and cotton in the United States. Schenkelaars et al. (2011) found that the maize, soybean, and cotton sectors in the United States had HHI scores well above 1,800 by 1999; that high score has continued into the 2000s.

Nevertheless, the ability of a firm to exercise market power may not imply that market power is having an adverse effect. Falck-Zepeda et al. (2000) showed that even though IR cotton adoption occurred in a market in which the firm that developed it had substantial market power—indeed, that firm was the only supplier of the technology—the innovator firm's share of additional benefits produced from *Bt* cotton adoption was similar to the share captured by producers that adopted *Bt* cotton. Kalaitzandonakes et al. (2010) and Kalaitzandonakes (2011) found evidence of moderate market power in the seed industry in the United States but also dynamic market efficiency derived from observed firm profits and investments in R&D, innovation, and product stewardship efforts from 1997 to 2008.

More research is needed to determine whether market power is affecting GE seed prices. Stiegert et al. (2010) showed that the prices of seeds with mul-

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[25] This situation in agricultural markets is not unique to crop seeds. Fuglie and Toole (2014) found similar levels of concentration in crop chemicals, animal health, farm machinery, and animal genetics.

tiple traits (also referred to as stacked traits, see Box 3-1) are lower than the sum of individually priced traits. The implication is that firms are attempting to capture additional gains from farmers by segmenting markets or bundling products with differentiated pricing mechanisms and demands or that economies of scale and scope are shaping seed markets. As Shi et al. (2008, 2010) have shown, the prices of individual traits were larger when added together than the prices of the stacked variety with all traits. Subadditive pricing, in which the sum of the individual traits is less than the stacked final product, is consistent with economies of scope in seed production. Economies of scope arise when it is cheaper to produce two products together than to produce them separately. Shi et al. (2009) showed increased market concentration as a causal factor in higher seed prices, but they also indicated that price increases may have been dampened by other market factors. Another issue that needs to be studied is how trait stacking may lead to the sale of more expensive seed than farmers might otherwise need. For example, a farmer might want only the HR trait in a maize variety but be unable to find a maize variety that does not also include *Bt* traits (see discussion of resistance evolution and resistance management in Chapter 4); this may lead to higher seed costs for the farmer in that the farmer does not need the added trait but is paying for it.

Increasing seed-market concentration has at least two potentially adverse outcomes. First, if the market is noncompetitive, farmers are likely to face higher than competitive market pricing. The 2010 National Research Council report on farm-level impacts of GE crops in the United States noted that seed prices increased dramatically for GE crops from 1994 to 2008. It also noted that various other factors—including yield increases, reduced expenditures on other inputs, labor savings, and improved weed control—outweighed the added costs (NRC, 2010a). However, research has not yet determined whether farmers would have even greater cost savings if the market for seeds were more competitive.

Second, market concentration in the hands of private firms may be a factor behind public concerns about GE crops. Studies have revealed varied public uncertainty and public trust in the institutions that are generating and testing GE crops and the food that is produced from them. For example, the public tends to trust university scientists, medical professionals, consumer-advocacy organizations, environmental organizations, and farmers but tends to have less trust in the federal government, mass-media sources, grocers, and the agricultural-biotechnology industry (Lang and Hallman, 2005; Lang, 2013). Huffman and Evenson (2006) picked up on variation in public trust when they observed that nearly all GE crops have been developed by agricultural-biotechnology firms to reduce costs for farmers. They contended that products from public-sector research that generated benefits for consumers "would do much to alleviate political concerns regarding [GE] foods" (Huffman and Evenson, 2006:285).

Because many of the largest firms developing GE crops are transnational corporations, the concerns about market concentration and the resulting social and economic consequences may extend to international markets. Those firms have aggressively sought to get international intellectual-property protections that are as strict as GE crop patents are in the United States (Strauss, 2009). According to Strauss (2009), the U.S. government's support and the efforts of leading firms that developed GE crops were two factors that led to the establishment of the 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights. Another implication is that, if U.S. patent policy is contributing to the curtailment of agricultural research, it is likely eventually to affect agricultural R&D globally (Jefferson et al., 2015).

Investment in Public Research

The 2010 National Research Council report on farm-level impacts of GE crops in the United States listed four kinds of contributions required of the public sector. First, the private sector lacks adequate incentive to focus on basic research because the time between research and application is often long; the public sector must meet this need. Second, a strong and independent public sector is needed to contribute to regulatory review of the products that private firms seek to market. Third, both public-sector and private-sector researchers have contributed and will probably continue to contribute to crop improvement. Fourth, as in the case of basic research, the private sector lacks adequate incentive to invest in minor and orphan crops;[26] GE crops are research-intensive and therefore expensive to create and promoting R&D in the public sector that focuses especially on generating public goods will be essential to generating GE crops that enhance economic, social, and ecological well-being broadly (NRC, 2010a).

Because of the private sector's lack of incentive to invest in research on minor and orphan crops, university and government researchers typically have been responsible for it. However, Welsh and Glenna (2006) found that, with the rise of GE crop research and university collaborations with the private sector to generate GE crops, university crop-research portfolios have begun to focus more on major crops than on minor crops. The shift in effort is probably related more to the passage of the 1980 Bayh-Dole Act, which enabled universities to claim title to inventions and to license them

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[26] The U.S. Food Quality and Protection Act of 1996 defined a major crop as a crop grown on more than 121,405 hectares (or 300,000 acres). Of the more than 600 crops grown in the United States, fewer than 30 qualify as major crops. The term *minor crop* applies to the rest. Orphan crops are those, such as cassava and cowpea, typically grown by resource-poor, small-scale farmers.

to the private sector, than simply to the increase in GE crop research. Since the passage of the act, U.S. universities have made modest revenues from technology transfers and licensing revenue; however, this has come at the cost of changes in university incentive structures (Huffman and Evenson, 2006). Because patented crops are expected to return licensing revenue to the university, policy-makers have been prone to use the returned money to justify reducing public support of research universities (Glenna et al., 2007). Huffman and Evenson (2006:291) suggested that the tradeoff may be beneficial for the university and the private sector, but they acknowledged that some of the changes made to attract private investment, research collaborations, and other private activities "may be seen as being in conflict with public interest or responsible behavior of a public institution."

There is a continuing debate over whether private funding and the pursuit of intellectual-property protections are crowding out public-interest research (Fuglie and Toole, 2014). Crowding out refers to the use of public funds to do research that should otherwise be done by the private sector. It can be used to describe such a scenario as when a university researcher who is collaborating with a private firm becomes more focused on generating private goods than on generating public goods or conducting public-interest research. Some research has indicated that many scientists who are involved in public–private research collaborations and who are generating intellectual property are also generating more public goods in the form of journal publications (Bonte, 2011) or that university research tends to complement industry research (Toole and King, 2011). If either is the case, crowding out is not occurring directly. However, other studies have found evidence of at least partial or temporary crowding out (Buccola et al., 2009) and in some cases substantial crowding out (Alfranca and Huffman, 2001; Hu et al., 2011). Huffman and Evenson (2006) noted that clear definition of public and private institutional responsibilities may reduce confusion and promote synergistic cooperation. However, they also stated that a greater involvement by universities in GE crops R&D would foster the proliferation of more public goods from GE crop research and might even help to "alleviate political concerns regarding [GE] food" (Huffman and Evenson, 2006:285). Schurman and Munro (2010) supported the latter perspective when they explained that active stakeholders may raise questions about the effects of GE crops on human health and the environment but really be more concerned about the ethical implications of patenting living things, private agricultural firms gaining a greater share of the agriculture and food system, whether industry scientists and regulatory agencies can be trusted when so much profit is at stake, whether universities and university scientists are shifting their research agendas toward the private interest at the expense of the public interest, and whether small farmers in industrialized and developing nations will be helped or harmed by the institutional arrangements that accompany the technology. Although the questions raised by active stakeholders cannot necessarily be generalized to the broader public, their concerns reflect underlying conflicting theories of justice that may provide an explanation of differences in perspectives about the value of GE crops. Social scientists have spent many decades in generating empirical evidence to further the ethical debates, even though the debates remain unresolved (Fuglie and Toole, 2014). More research, policy-maker attention, and public deliberation are needed to determine whether new policies and resources should be directed at contributing to the social welfare derived from GE crops.

King and Heisey (2007) made a strong case for supporting the generation of public knowledge in agricultural R&D, particularly as related to GE crops. Their research indicated that vibrant public research institutions have yielded important social benefits. Lopez and Galinato (2007) used data from rural Latin America to contrast the social benefits that resulted from public subsidies for the creation of private goods with the benefits that resulted from public investment in the creation of public goods. Their findings supported findings of studies around the world that public subsidies for private goods fail to lead to higher investments, employment, or productivity, whereas rates of return on funding for public goods are high. After a review of research into crop-productivity gains during the 20th century, Piesse and Thirtle (2010:3036) concluded that the crop-productivity achievements "required massive and sustained expenditures on R&D" and that there is "no doubt that R&D expenditures have led to these productivity gains." Conversely, although private expenditures on plant breeding increased by nearly 250 percent in real dollars from 1980 to 1996 (Heisey et al., 2002), Fuglie et al. (2012) found that private-sector R&D does not contribute to agricultural productivity.

Of course, crop-productivity gains do not equally enhance social welfare for everyone inasmuch as greater yields can depress commodity prices to the detriment of farmers. However, enhanced agricultural productivity can contribute to greater availability of food for many people and thus enhance social welfare. A substantial portion of the productivity gains has resulted from public funding of research in public institutions, and that funding can lead to what might be thought of as stocks of knowledge that can be drawn on later. One study estimated the total investment in the United States in 1850–1995 and found that the stock of agricultural knowledge in the United States in 1995 was 11 times more than the actual agricultural output for that year; that is, every $100 of agricultural output was developed by drawing on $1,100 in stock of knowledge (Pardey and Beintema, 2001). The point of these calculations was to demonstrate that scientific knowledge is cumulative and that many years of public investment in scientific research are drawn on in each year of agricultural development, especially because new crop varieties typically take 7–10 years to develop. Specifically in the case of GE crops, research indicates that universities tend to do the basic research, start-up companies apply the findings, and large companies intervene to move the applications to commercialization (McMillan et al., 2000; Graff et al., 2003). Findings from other research indicate that U.S. university scientists wrote nearly three-fourths of the papers cited in agricultural-biotechnology patents (Xia and Buccola, 2005). Vanloqueren and Baret (2009) noted that studies like those demonstrate how important publicly funded scientific research is for agricultural innovation.

Bozeman (2002) warned that overreliance on market mechanisms can lead to a scarcity of providers of public goods. The trend in agricultural research toward the private-sector model rather than the public-sector model is of particular concern for the United States because, according to estimates by Alston et al. (2010), the United States accounted for nearly one-fourth of the world's agricultural and food R&D in 2000. Thus, institutional changes that affect crop R&D in the United States are likely to have global effects. A decline in public-research investment may mean a decline in informative scientific endeavors that are not likely to yield a private return on investment, such as research on subjects related to broad understanding of social welfare and equity, self-pollinated and minor crops, and human and environmental well-being (Huffman and Evenson, 2006; Fuglie and Toole, 2014). If the public sector is going to make these necessary contributions to public-interest research, government support for that research will need to be increased.

FINDING: There is disagreement in the literature as to whether patents facilitate or hinder university–industry knowledge-sharing, innovation, and the commercialization of useful goods, and utility patents on GE crop germplasm legally block research on a crop.

FINDING: Whether a patent is applied to conventionally bred or GE crops, 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.

FINDING: There is evidence that the portfolio of public institutions has shifted to mirror that of private firms more closely.

RECOMMENDATION: More research should be done to document benefits of and challenges to existing intellectual-property protection for GE and conventionally bred crops.

RECOMMENDATION: More research should be done to determine whether seed-market concentration is affecting GE seed prices and, if so, whether the effects are beneficial or detrimental to farmers.

RECOMMENDATION: Research should be done on whether trait-stacking is leading to the sale of more expensive seeds than farmers need.

RECOMMENDATION: Public investment in basic research and investment in crops that do not offer strong market returns for private firms should be increased.

Food Security

Several authors have proposed that genetic-engineering technology can be a key tool in solving hunger in the world (for example, Borlaug, 2000; Fedoroff, 2011; Juma, 2011). The evidence reviewed indicates that GE crops may be a means of contributing to crop-productivity gains (Anthony and Ferroni, 2012), but the effect of GE crops on hunger will depend on development of appropriate crop varieties and the appropriate political, social, and cultural context. As was discussed in Chapter 4, no GE food crop has a commercial record of increasing the potential yield of a crop; GE crops that have affected yield have done so by protecting yield. At the subsistence-agriculture level, protection of yield from biotic stresses (insects and pathogens) and abiotic stresses (drought and temperature extremes) should decrease the year-to-year variation in food availability, and that is important in preventing hunger. GE crops that have already been commercialized have the potential to protect yields in places where they have not been introduced, and GE crops in development, such as those reviewed earlier in this chapter in the section "Prospects and Limitations for Genetically Engineered Crops in Development for Small-Scale Farmers" may protect yields of a wider array of crops (for example, disease-resistant cassava and climate-resilient rice). However, as was also discussed in that section, 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. All farmers will need tools to deal with increasing constraints on resources (Box 6-8). As Glover (2010:6) noted, "Gene splicing is not intrinsically capable of surmounting obstacles like poor roads, inadequate rural credit systems and insufficient irrigation." Nonetheless, increased yield potential and increased nutritional quality are important

BOX 6-8
Constraints on Resources in Agriculture

All agricultural production is limited by the availability of resources, such as arable land, water, and favorable climate conditions. Evidence reviewed by the committee suggested that constraints on those resources were already affecting global agricultural production in 2015.

For example, the Food and Agriculture Organization (FAO, 2013) reported that many countries do not have available arable land on which to expand farming. In countries that do have available arable land, expansion may come at the expense of forests and grasslands (FAO, 2011). Environmentally sustainable growth in agricultural production, regardless of the method used, will therefore have to come from an increase in yields rather than from an increase in cultivated land.

All farming systems need water, either from precipitation or from irrigation. Most of the world's cropland is rainfed. Rainfed agriculture produces about 60 percent of the world's crops; irrigated agriculture makes up the balance. The global freshwater withdrawal rate from such sources as rivers and aquifers is less than 10 percent.[a] However, withdrawal rates vary by location; the withdrawal rate is 20 percent in Asia and over 200 percent in northern Africa (FAO, 2011). More than 40 percent of the world's rural population lives in places where water is scarce, irrespective of the method of farming practiced (FAO, 2011).

Climate change will probably exacerbate water-supply issues for rainfed and irrigated farmland. Some regions will become drier and others wetter, with increasing unpredictability of precipitation and seasons and more frequent extreme weather events (IPCC, 2014). Those events will also include greater swings in temperature. Heat waves and extended cold snaps will affect potential yields.

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[a] Total available freshwater is based on the long-term average annual flow of rivers and recharge of aquifers generated from endogenous precipitation. See "Internal Renewable Water Resources" at http://www.fao.org/nr/water/aquastat/data/glossary/search.html. Accessed December 7, 2015.

for smallholders. Chapter 8 addresses the potential for genetic-engineering technology to increase potential yield and enhance nutritional traits.

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 (Tripp, 2009a). There are more GE crop developers emanating from developing countries, especially, India and China, but also African countries (Parisi et al., 2016), and this holds promise that future GE crops will be developed with specific regions, countries, or farmers in mind, thereby improving productivity or nutritional content unique to a region. The complex problems associated with smallholder farmers and food-insecure consumers need to be addressed if food insecurity is to be reduced. There is enough food in the world today, but about 1 out of every 9 people do not have enough food to eat (FAO, 2015). GE crops can contribute to a broader food-security strategy, but complex problems, like food insecurity, require "multi-pronged solutions" (Qaim and Kouser, 2013:7).

> **FINDING: The ability of crops with GE traits to address food-security concerns will depend on the types of traits introduced and the social and economic contexts in which the traits are developed and diffused.**

CONCLUSIONS

There is a tremendous amount of diversity in the world's farmers, the types of crops that they grow, and the conditions under which they grow those crops. Introducing genetic-engineering technology into the mix creates the potential for distinct social and economic effects.

Having reviewed the literature available on social and economic effects, the committee finds that the research on the topic is not sufficient. Much of the literature focuses on one or two trait–crop combinations and does not have sufficient coverage especially of new crops in the R&D pipeline. There has been little or no investigation of the return on investment in genetic engineering versus alternative investment aimed at low external input technologies (LEIT), such as agroecological improvements. Tripp (2006) observed that, without the development of more robust institutional capacity to meet the needs of small farmers, LEITs are no more likely to benefit smallholder farmers than GE crops. However, after a critical review of various reports and arguments in favor of LEIT, Tripp (2006:209) concluded that "there is no doubt that support for this kind of technology development needs to be sustained and increased." A more systematic study of farmer knowledge would be useful as would more information on whether the concentration of the seed market is affecting farmers' options and welfare.

On the basis of the research that is available, the committee concludes that existing GE crops have generally been useful to large-scale farmers of cotton, soybean, maize, and canola. The same GE crops have benefited a number of smaller-scale farmers, but benefits have varied widely across time and space, and are connected to the institutional context in which the crops have been deployed. Small-scale farmers were more likely to be successful with GE crops when they also had access to credit, extension services, and markets and to government assistance in ensuring an accessible seed price.

Genetic-engineering technology that is of most use to small-scale farmers or farmers of specialty crops will probably have to emerge from public-sector institutions or from public–private collaborations because current intellectual-property regimes do not offer incentives for private-sector firms to pursue research in those crops. However, growth in investment in public agricultural research in the United States has been declining since the 1960s and was almost $2 billion less than private-sector investment in 2009 (NRC, 2014). In developing countries, the situation regarding R&D investment is highly variable. In some countries, investment in public sector R&D has increased substantially; in others it has not. Furthermore, there has been a rise in development assistance focused on agriculture, including investment in genetic engineering. Decreases in support for the public sector may reduce the potential diffusion of new GE crop innovations.

To contribute to alleviation of hunger in food-insecure populations on and off farms, more GE crops and GE traits will need to be developed in ways that increase potential yield, protect yield from biotic and abiotic stresses, and improve nutritional quality. Even if that is accomplished, the ability of GE crops to alleviate hunger will depend on the social and economic contexts in which the technology is developed and diffused.

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7

Future Genetic-Engineering Technologies

This report has focused thus far on the "experiences" aspect of the committee's statement of task. The purpose of the present chapter is to consider the "prospects," that is, how genetic engineering might be used in the future in agricultural crops. That includes speculation about future genetic-engineering technologies.

To provide a context for genetic engineering in overall crop improvement, the chapter first provides a description of plant-breeding methods and of genomics approaches that enable rapid advances in basic knowledge related to crop genetics and plant breeding. It then discusses commonly used genetic-engineering technologies, examining the breadth and depth of current use and current limitations. Next, it scans the horizon for emerging genetic-engineering technologies, including synthetic biology and genome editing, and speculates about how they might shape the future of crops. The expected applications of genome editing and the technologies available for assessing associated nontarget effects are discussed in more detail.

Finally, "-omics" (genomics, transcriptomics, proteomics, metabolomics, and epigenomics) approaches are reviewed to evaluate their potential to assess intended and unintended effects of genetic engineering and conventional plant breeding. The committee concludes that advances in genetic engineering and -omics technologies have great potential to enhance crop improvement in the 21st century, especially when coupled with advanced conventional-breeding methods.

MODERN PLANT-BREEDING METHODS

Conventional plant-breeding approaches rely on the selection of plant germplasm with desirable agronomic and product characteristics (that is, phenotypes) from among individual plants created by using crosses and mutagenesis. Breeding used to be entirely phenotype-based; that is, plants were selected solely on the basis of features such as yield, without knowledge of the genetic composition of the plants. All plants of potential interest would be grown, phenotyped, and harvested, all of which are time-intensive and resource-intensive. The entry of molecular biology into breeding programs in the 1980s enabled knowledge of genetic determinants of phenotypes and marker-assisted selection (MAS) in which DNA-based molecular markers are used to screen germplasm for individual plants that have desired forms of genes, known as alleles. MAS reduced plant sample sizes needed to select desirable individual plants and has been used in many crops to reduce costs and increase efficiency. MAS allows the identification and elimination of an individual plant from a population on the basis of its genetic composition and, as a consequence, reduces the costs associated with both continued propagation and downstream phenotyping (Ru et al., 2015). For example, before MAS, each tree in a fruit-tree breeding program had to be grown for years before it would produce fruit that could be phenotyped. However, molecular markers associated with self-compatibility (in which fertilization does not require outside donor pollen) and fruit size have recently been used to eliminate seedlings that lack alleles favorable for these two critical market traits in a sweet cherry (*Prunus avium*) breeding program, resulting in substantial savings (Ru et al., 2015). MAS does not require knowledge of the specific genes that confer a trait; it only requires markers that are tightly associated with a trait, which may or may not be within the gene controlling the trait (see, for example, Box 7-1). MAS is not used in all plant-breeding programs, but its use might soon become universal as more genetic information is made available and screening costs are reduced.

As in all other disciplines of biology, plant breeding is now in the genomics era, in which paradigm-changing methods are being incorporated to accelerate and improve the efficiency of breeding. Incorporation of genomics into breeding and genetics research has resulted in an increased knowledge base on crop genetics, species diversity, the molecular basis of traits, and the evolutionary history of crop origins from primitive wild species. MAS and genomics greatly reduce the number of individual plants that need to be retained in the breeding pipeline for phenotyping. Genome-level datasets and genomic technologies have been used to identify causal genes, alleles, and loci important to relevant agronomic traits and have thereby become tools to accelerate breeding cycles (Box 7-1).

BOX 7-1
A Sequenced and Assembled Genome Advances Basic Biological Knowledge

Access to the genome sequence of even one individual of a species, known as the reference genome, has advanced basic knowledge of the genes and alleles that govern traits and, as a consequence, facilitated the identification of DNA markers for marker-assisted selection (MAS). An example is potato, a staple crop for which breeding is challenging. Potato is native to the equatorial regions in the Andes, where tuber development depends on short days. However, a key trait that led to high-yielding potatoes in regions with long summers (including Europe and North America) was tuber development under long days. Genetic mapping revealed a major quantitative trait locus—the maturity locus—on chromosome 5 that controlled tuber initiation (Visker et al., 2003). Access to the potato genome sequence permitted identification of the allelic variants of the gene that controls tuber initiation, which not only provided a clear connection between tuberization, the circadian clock, and the tuberization signal but provided a molecular marker for use in MAS to identify varieties adapted to specific geographic regions (Kloosterman et al., 2013).

An array of genomic technologies can be used to generate large-scale genetic-diversity data on any species that can be used to breed improved crop varieties through such techniques as MAS. For example, genome sequencing and resequencing (in which all or part of the genome is sequenced) and single-nucleotide polymorphism (SNP) assays (in which hundreds to millions of individual loci are assayed for allelic diversity) are genomic methods that are used routinely in many crops. Several technological approaches can be applied to assay SNP loci, including platforms that use mass spectrometry, primer extension, or reduced-representation targeted resequencing to assay the polymorphism. Major considerations for the plant breeder in the choice of technological platform are marker density, sample throughput, cost, and number of loci to assay. Depending on the crop, a publicly or commercially available SNP platform is used, as are custom SNP arrays for specific applications.

The coupling of continual advancements in genomic technologies with increased throughput and decreasing costs means that conventional and genetic-engineering breeding programs now have access to a wealth of genetic-diversity data that can be used to link genes (and alleles) with phenotypes and agronomic traits. For example, large-scale, genome-diversity data on several major crops have been generated, including not only cultivated lines but related wild species and landraces. The information has provided insights into the genetic and molecular basis of agronomic traits, genetic bottlenecks that restrict major improvements in breeding gains, and key genes and events in domestication and crop improvement, all of which lead to more efficient breeding (Huang et al., 2010; Lam et al., 2010; Chia et al., 2012; Hufford et al., 2012; Jiao et al., 2012; Li et al., 2014b; Lin et al., 2014).

At the time when the committee's report was being written, a reference genome of nearly every major crop species was available. The quality of the reference genome sequences varies substantially, depending on technical and cost limitations. A complete genomic sequence with few or no gaps is the "gold standard" for a reference genome, but incompletely characterized genomes are also useful. For many crops, diversity panels[1] with their associated genome and phenotype datasets have been or are being developed. However, the availability of large-scale genetic information is not a panacea for plant breeding. A reference genome derived from a single individual or genotype does not provide full representation of the genome information needed for crop improvement; as a consequence, multiple reference genomes for each species are needed to adequately capture the genome diversity. For various reasons—including lack of access to data, lack of computational tools, and insufficient analytical expertise in genomics—some researchers do not take full advantage of genomic data. However, as genomic technologies improve so that any individual plant's genome can be sequenced and analyzed, as breeders acquire more expertise in using relevant genomic and bioinformatic technologies, and as genotyping methods improve in throughput and cost efficiency, those limitations will be overcome, and this will leave phenotyping as the major limitation of efficient breeding. Thus, it is likely that high-throughput, field-based phenotyping technologies will be developed to provide parallel datasets, increase efficiency, and reduce costs associated with breeding.

FINDING: Conventional and genetically engineered plant-breeding approaches in the 21st century have been enabled by increased knowledge of plant genomes, the genetic basis of agronomic traits, and genomic technologies to genotype germplasm.

FINDING: Continued improvements in genomic technologies and algorithm and software development in the coming decades will facilitate further improvements in the efficiency of plant breeding.

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[1] Diversity panels are collections of germplasm that represents a crop species. The panels include cultivars, landraces, and wild species related to the crop that collectively represent the genetic diversity of the crop or can be used to improve phenotypic traits in the crop.

FINDING: As genomic technologies increase in throughput and decrease in cost, thousands of genomes will be characterized per crop species.

COMMONLY USED GENETIC-ENGINEERING TECHNOLOGIES

This section reviews widely used genetic-engineering technologies that have been applied in the development of commercialized genetically engineered (GE) crops.

Expression of Added Genes

Since the application of recombinant-DNA technology to plants in the 1980s, most of the technology deployed commercially has consisted of constant or constitutive expression of transgenes in a few crop species in which *Agrobacterium*-mediated or gene gun-mediated transformation is used to insert a specific gene of interest into a random location in the plant nuclear genome. A single gene that endows a simple trait, such as the production of an enzyme that confers herbicide resistance or a *Bt* toxin for insect resistance, is incorporated into all the cells of the plant. In addition to the single transgene of interest, a selectable marker gene is sometimes included in the same DNA molecule that is transferred into the plants to facilitate identification of plants that have the transgene of interest. This type of "one-gene" genetic engineering was exemplified in most commercialized crops grown in 2015.

Transgenics versus Cisgenics versus Intragenics

Because of legislative, regulatory, marketing, and public-perception concerns, efforts have been made to develop GE crops with genes found in a crop species of interest or a plant species that can naturally interbreed with it (Rommens, 2004); this has become known as cisgenesis (Schouten et al., 2006). In the strictest definition of cisgenesis, an entire native gene would be cloned intact from a different variety of the crop or a sexually compatible relative and inserted into the genome of the crop of interest. In a related approach called intragenesis, the researcher recombines various plant DNAs, all of which came from the crop or its relatives into a single genetic construct to be introduced; for example, the promoter could come from one gene and the coding region from another gene (Holme et al., 2013). Several cisgenic–intragenic GE crops have been developed and field-tested. At the time the committee's report was being written, only one intragenic crop species, the Innate™ potato developed by Simplot Plant Sciences, had been approved for commercialization.

Nuclear Genome Transformation versus Plastome Transformation

All plant cells have three separate genomes. The largest is in the nucleus, which contains hundreds of millions to billions of nucleotide bases.[2] Much smaller genomes are in the mitochondria and plastids (hundreds of thousands of bases each). The plastid genome is known as the plastome.

As discussed above, almost all GE crops sold at the time the committee's report was being written had been created with recombinant-DNA technology using *Agrobacterium*-mediated or gene gun-mediated nuclear genome transformation methods. Whereas gene gun-mediated transformation theoretically results in the possibility of transforming any of the three genomes, *Agrobacterium* favors gene transfer into the nuclear genome of plants (Zhang et al., 2007). As discussed in Chapter 3, nuclear genome transformation has proved to be successful in a wide array of plant taxa.

Plastome transformation was developed in the 1980s and was enabled by the invention of the gene gun (Svab et al., 1990). Plant mitochondrial genomes have not yet been transformed. As an alternative to nuclear genome transformation, plastome transformation has several advantages over nuclear transformation (Maliga, 2003; Jin and Daniell, 2015). First, transgenes are targeted to a specific locus in the plastome by using homologous recombination; thus, there are no "position effects" that influence gene expression. Second, extraordinarily high concentrations of recombinant protein can be produced; for example, *Bt* Cry2A accumulated to 46 percent of total soluble protein when the gene was localized in the plastome of tobacco (De Cosa et al., 2001). Third, most plant species are characterized by maternal inheritance of plastids, which could address transgene bioconfinement goals (Daniell, 2002); because most pollen does not contain plastids, concerns about gene flow are eliminated or reduced.

In spite of those advantages, some notable hurdles have prevented plastome transformation from being widely used in crops (Maliga, 2003). First, because there are thousands of plastomes per plant cell, it is not trivial to achieve homoplasmy, in which all plastomes in the cell have an identical GE change. An effective tissue-culture protocol is required to rid chloroplasts of native, untransformed plastomes. Thus, relatively few species (mostly in the Solanaceae family, such as tobacco, potato, and tomato) are amenable to tissue culture and have been routinely subjected to transplastomic methods. Second, few selectable marker genes and antibiotic combinations are effective for obtaining transgenic and homogeneous (transplastomic homoplasmic) cells. Nonetheless, there is tremendous

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[2] See Chapter 3 (section "The Development of Genetic Engineering in Agriculture") for how the four nucleotide bases adenine, guanine, thymine, and cytosine form the structure of DNA.

interest in expanding the use of plastomes transformation in various crop species, especially when high transgene expression is desired.

Antisense or RNA Interference Approaches to Decrease Gene Expression

In delivering agronomic traits of interest by using genetics, the simple add-new-DNA-and-protein approach has been successful. However, silencing the expression of one or more native genes in plants or silencing the expression of pest genes, such as those found in pathogens or herbivorous insects, is sometimes desired.

The first method that was used to decrease the expression of genes in GE plants is termed antisense silencing. In an antisense gene construct delivered into the plant genome, the gene to be downregulated (that is, silenced) is essentially put in "backwards" into a plant transformation vector. When the backwards gene is transcribed, the messenger RNA (mRNA) produced from the transgene interferes with the translation of complementary mRNA of the gene to be silenced in the plant or pest into protein (or it can lead to RNA interference, described below). The FLAVR SAVR™ tomato is one of the first examples of the use of antisense technology to produce a GE crop; the FLAVR SAVR tomato had the desirable trait of altered fruit ripening and enhanced fruit quality owing to interference with the expression of the gene that encodes the polygalacturonase enzyme (Kramer and Redenbaugh, 1994).

A second method of silencing gene expression was developed in the late 1990s on the basis of fundamental biological research in plants: RNA interference (RNAi). RNAi started to be used extensively to genetically engineer plants in the 2000s as plasmid vectors and more plant-specific biological information became available. It had been known since the earliest days of plant biotechnology that post-transcriptional gene regulation (silencing) was an important process that could regulate the level of expression of plant genes. For example, it was thought that overexpression of a gene important in the anthocyanin pigment production pathway in petunias would produce flowers that had more rich purple pigmentation; instead, the resulting petunia flowers were white (Napoli et al., 1990). Unbeknownst to the researchers and to the producers of FLAVR SAVR tomato, the RNAi mechanism was the cause of gene silencing; that is, attempts at antisense silencing or overexpression triggered the RNAi mechanism (Krieger et al., 2008). Whereas the actual mechanism of RNAi was first mechanistically elucidated in nematodes (Fire et al., 1998, which resulted in the award of a 2006 Nobel prize to Craig Mello and Andrew Fire), RNAi is now known to be a natural molecular pathway that all higher organisms use to defend themselves against parasites and pathogens.

For uses in GE crops, noncoding RNA production in the form of double-stranded RNA (dsRNA) is an efficient way to set off a cascade of molecular events within the cell to silence genes in the target plant gene or pest gene of interest, which can result in a new trait. Such traits can involve reduced lignin in plant cell walls, decreased browning in apples, or insect resistance (see Chapter 8). RNAi transformation vectors used for plant transformation are designed to allow the production of an mRNA molecule that will fold back on itself (hairpin RNA) to produce dsRNA. The RNAi machinery in the plant processes the dsRNA to produce 21- to 23-nucleotide small interfering RNA (siRNA) that ultimately targets the mRNA of interest for destruction. The degraded mRNA cannot be translated into protein, so a new trait is created. When the committee's report was being written, RNAi was being used extensively as the primary tool in plant biology for silencing the expression of endogenous genes and was beginning to be used in commercial GE crops (see Chapter 8).

A notable use of RNAi, published in two papers in 2015 (Jin et al., 2015; Zhang et al., 2015), sought to engineer insect-pest resistance in crops. The researchers used a novel approach, which was to make dsRNA via transgenic chloroplast genomes (plastomes) in crops that were often subjected to damaging herbivory by insects. The dsRNA was designed to trigger the RNAi pathway in the insects that consume the GE plant. The method was effective for two reasons. First, the dsRNA cannot be processed within the plastids because the RNAi machinery does not exist in plastids, thereby ensuring the presence of intact dsRNA in the GE plant when the insect feeds on the plant. When the insect consumes intact dsRNA designed to target a vital insect gene, the gene's expression in the insect is silenced, killing the insect. Second, plastome expression provides high expression of the dsRNA relative to that possible by nuclear transformation (discussed above). An important consideration in using this technique is to design dsRNAs and their component siRNAs highly specific to the target gene to avoid effects on nontarget genes. As with any genetic engineering-based insect-control strategy, potential nontarget effects need to be investigated.

Development of Non–Tissue-Culture Transformation Methods

As described in Chapter 3, the construction of GE plants commonly relies on in vitro plant tissue culture, transformation, and plant regeneration. Among the complications often associated with the regenerated plants is that they can be variable in phenotype and fertility because of somaclonal variation rather than the genetic-engineering event itself (see Chapter 3 for description of somaclonal variation). Many factors—including crop, culture media, length of time in tissue culture, and genotype—can affect the frequency and severity of somaclonal variation. Altered gene expression can result from changes in chromosome number or structure, in DNA sequence, in epigenetic status—for example, DNA methylation (see below)—or in all the above (Jiang et al., 2011; Stroud et al., 2013). Because tissue-culture–derived GE plants, also known as transformants, are potentially subject to the effects of somaclonal variation on any gene or transgene and to positional effects on the degree and stability of transgene function, researchers routinely screen multiple independent transformants to select individual "events" that do not display aberrant phenotypes.

There are a few notable exceptions to the requirement of tissue culture for plant transformation. One is the floral-dip method. Some members of the Brassicaceae family, such as *Arabidopsis thaliana* and *Camelina sativa*, can be transformed with the floral-dip method (Clough and Bent, 1998; Liu et al., 2012), in which *Agrobacterium tumefaciens* delivers the transgene directly into the genome of egg cells, thereby permitting production of transgenic plants directly from seed. Numerous laboratories have attempted to adapt the floral-dip method to other species, but results have not been reliable or reproducible. Another is the use of particle bombardment to directly transform cells in plant organs that can be rapidly regenerated into plants; this avoids a prolonged cell-culture phase in which somaclonal variability can accumulate (Christou, 1992).

It is well known that, if a plant is grafted, RNAs and proteins can move between the rootstock and the scion; thus, in a grafted plant with a transgenic rootstock or a transgenic scion, there is the potential for GE-derived molecules to be transported to non-GE portions of the plant (Haroldsen et al., 2012). For example, if a rootstock were transgenic then fruits might have products of the transgene.

> **FINDING: Construction of GE plants commonly relies on in vitro plant tissue culture that can result in unintended, somaclonally induced genetic change. Development of transformation methods that minimize or bypass tissue culture for all crop species would reduce the frequency of tissue-culture–induced somaclonal variation.**

EMERGING GENETIC-ENGINEERING TECHNOLOGIES

In addition to the technologies discussed above, new genetic-engineering approaches have been developed and are being refined and improved. Although they have not been applied to commercial products yet, they hold practical value for future GE crops. The technologies include genome editing, synthetic DNA components and artificial chromosomes, and targeted epigenetic modifications.

Genome Editing

Genome editing uses site-directed nucleases (sequence-specific nucleases; SSNs) to mutate targeted DNA sequences in an organism. Using SSN systems, scientists can delete, add, or change specific bases at a designated locus. SSNs cleave DNA at specific sites and leave a single break (known as a nick) or a double-strand break. The DNA break can be repaired in two ways (Figure 7-1):

- Through the cell's native nonhomologous end joining (NHEJ) process, which leads to a mutation at the site.
- If a donor DNA molecule is provided at the same time as the DNA is being edited by the nucleases, through the cell's own native DNA repair machinery—known as homology directed repair (HDR)—which incorporates the donor molecule at the cleavage site.

Four main classes of SSNs are used in plant genome editing (reviewed in Voytas and Gao, 2014): meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 nuclease system (Figure 7-2). The field of genome-editing technologies and application has burgeoned, especially since the advent of the CRISPR/Cas9 system, and the committee expects additional discoveries to facilitate genome editing in the coming decade.

Meganucleases naturally occur in bacteria, archaea, and eukaryotes and were the first SSNs examined for genome editing. Meganucleases are single proteins that recognize a sequence in the DNA that is at least 12 nucleotides long and cleave the target DNA, leaving a double-strand break that can be repaired through NHEJ or HDR by using a donor molecule (reviewed in Silva et al., 2011). Meganuclease-mediated genome editing has been demonstrated in maize (*Zea mays*) and tobacco (*Nicotiana* spp.) (reviewed in Baltes and Voytas, 2014). It is difficult to change the target sequence specificity of meganucleases, so they are not widely used for genome editing.

Zinc finger–domain-containing proteins bind to DNA and are widespread in nature, often functioning as transcription factors (proteins that regulate gene expression by binding directly or indirectly to regulatory DNA sequences usually found in the promoter regions of genes[3]). The zinc finger domains can be manipulated to bind specific sequences of DNA; when fused to the DNA-cutting nuclease domain of the FokI protein, a ZFN is the resulting hybrid molecule. A pair of ZFNs functions in tandem

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[3] Examples of genetic engineering using transcription factors are given in Chapter 8.

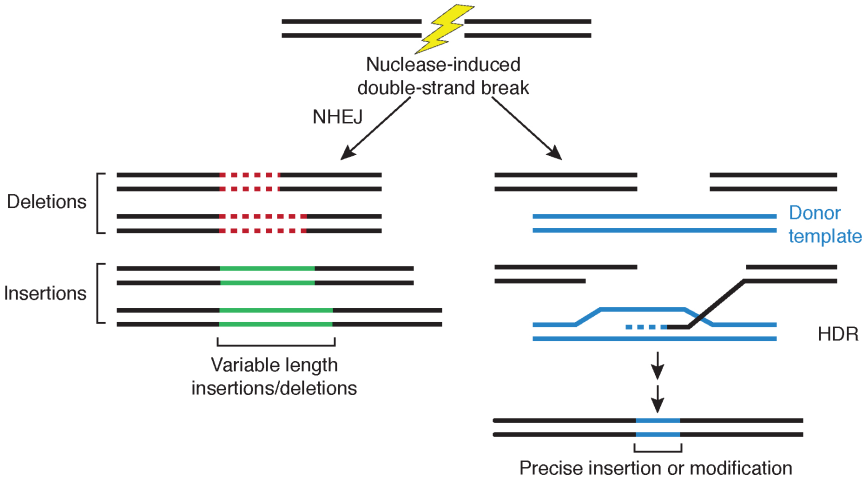

FIGURE 7-1 Consequences of DNA cleavage by genome-editing technologies in the cell.
SOURCE: Sander and Joung (2014).
NOTE: After cleavage of double-stranded DNA by sequence-specific nucleases such as meganucleases, zinc fingers, transcription activator-like effectors, and clustered regularly interspaced palindromic repeats/Cas9 (represented by the lightning bolt), the double-strand break in the DNA molecule can be repaired through native non-homologous end joining (NHEJ) mechanisms of the cell, which leads to an altered DNA sequence with either a deletion (dotted red line) or an insertion (solid green line). If a donor DNA template is provided (see blue DNA fragment), the homology-directed repair (HDR) mechanisms within the cell will insert the donor molecule into the locus, and this leads to an edited gene or target region (blue region with a precise insertion or modification).

to cut DNA at the desired target site (reviewed in Urnov et al., 2010). As with meganucleases, ZFNs are used for introducing mutations through NHEJ and HDR. ZFNs have been used in engineering of numerous plant species (reviewed in Baltes and Voytas, 2014). ZFNs were the first widely used designer genome-editing tool in biology.

Transcription activator-like effectors (TALEs) were discovered in the bacterial plant pathogen *Xanthomonas* and could be engineered to bind to virtually any DNA sequence. Their ease of design for specific target DNA sequences revolutionized genome editing. In nature, *Xanthomonas* species secrete TALEs into plant cells to enable pathogenicity. TALEs bind to promoters in plant genes to suppress the plant's resistance to the pathogen. The bacteria encode TALEs through a simple code or cipher that has been

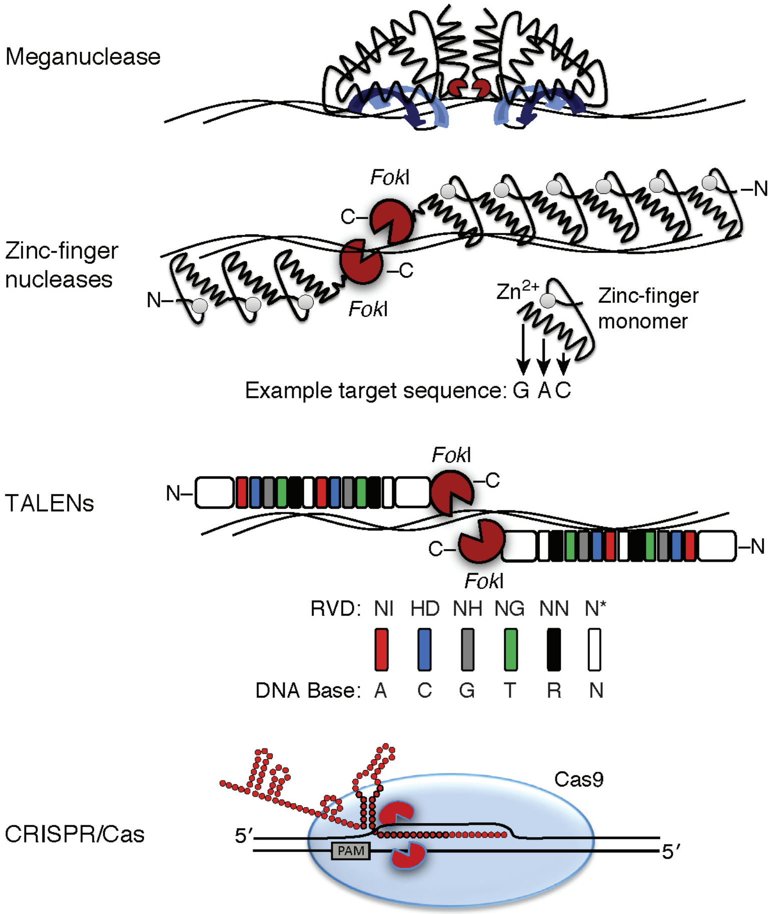

FIGURE 7-2 Genome-editing technologies: Meganucleases, Zinc finger nucleases (ZFNs), Transcription activator-like effector nucleases (TALENs), and Clustered regularly interspaced palindromic repeats (CRISPR)/Cas.
SOURCE: Baltes and Voytas (2014).

exploited to engineer proteins with custom site specificity in any target genome (Boch et al., 2009; Moscou and Bogdanove, 2009). Like ZFNs, TALEs can be fused with the nuclease domain of FokI and are then referred to as TALENs. TALENs are used in pairs like ZFNs to affect targeted mutations. TALENs have been used to edit genomes in several plants, including rice (*Oryza* spp.), maize, wheat (*Triticum* spp.), and soybean (*Glycine max*) (reviewed in Baltes and Voytas, 2014).

CRISPR was the most recently developed genome-editing tool when the committee's report was being written. Bacteria harbor CRISPR as an innate defense mechanism against viruses and plasmids that uses RNA-guided nucleases to target the cleavage of foreign DNA sequences. At the time the committee's report was being written, the CRISPR/Cas system used in genome editing was primarily the Type II CRISPR/Cas9, from *Streptococcus pyogenes*, in which foreign DNA sequences are incorporated between repeat sequences at the CRISPR locus and then transcribed into an RNA molecule known as crRNA (reviewed by Sander and Joung, 2014). The crRNA then hybridizes with a second RNA, the tracrRNA, and the complex binds to the Cas9 nuclease. The crRNA guides the complex to the target DNA and, in the case of innate immunity in bacteria, binds to the complementary sequence in the target DNA that is then cleaved by the Cas9 nuclease. Scientists have dissected the innate CRISPR/Cas9 system and re-engineered it in such a way that a single RNA, the guide RNA, is needed for Cas9-mediated cleavage of a target sequence in a genome. Guide RNA design requirements are limited to a unique sequence of about 20 nucleotides in the genome (to prevent off-target effects) and are restricted near the protospacer adjacent motif sequence, which is specific for the CRISPR/Cas system. Newer applications of CRISPR include the use of two unique guide RNAs with a modified nuclease that "nicks" one strand of the DNA, providing greater specificity for targeted deletions. The ease of design, the specificity of the guide RNA, and the simplicity of the CRISPR/Cas9 system have resulted in rapid demonstration of the utility of this method of editing genomes in plants and other organisms (reviewed in Baltes and Voytas, 2014). Genome editing, especially CRISPR, is changing rapidly. At the time the committee's report was being written, non-Cas9 endonucleases (for example, Cpf1) had been recently described for CRISPR genome editing (Zetsche et al., 2015).

When the committee was writing its report, applications of SSNs in genome editing had been used mostly to introduce mutations at the target locus through NHEJ to produce gene knockouts. As shown in Figure 7-1, nucleases can also be used for sequence replacement via HDR (or potentially NHEJ) if a donor DNA is co-introduced into the cell. Multiple types of donor molecules can be used. First, an alternative allele of the target locus can be introduced in such a way that the modified gene encodes a protein that confers a novel or enhanced trait. For example, modification of a specific single nucleotide in the acetolactate synthase (ALS) gene can confer resistance to herbicides that use ALS inhibition as their mode of action (Jander et al., 2003). Second, homologous recombination can be used to introduce a novel sequence at that locus. This "precision genome insertion" by engineering of a landing site would eliminate the semirandom insertion of transgenes in *Agrobacterium*-mediated and gene gun-mediated transformation methods. It would also permit combining of modified or edited genes at a single locus, termed "trait landing pads," in the genome rather than randomly in the genome, so it would be easier to add new traits to a GE crop that are physically linked in the genome (Ainley et al., 2013). This strategy would also enable the removal of inserted genes when desired.

Genome editing via CRISPR and other techniques might be performed in plants via transient expression of transgenes (Clasen et al., 2016) or without exogenous DNA at all (Woo et al., 2015) resulting in GE plants that lack the transgene. Clasen et al. (2016) used a genetically encoded TALEN pair to produce specific mutations in potato protoplasts. Potato plants recovered from the protoplasts with mutated targeted alleles contained a new quality trait, and seven of the 18 GE lines did not contain any TALEN transgene constructs in the potato genome. Woo et al. (2015) used in vitro–translated Cas9 protein coupled to guide RNA to mutate genes in *Arabidopsis*, tobacco, lettuce, and rice protoplasts, from which mutated plants were recovered. Thus, it appears that genome editing can be performed in crops without leaving any transgenic DNA footprint in the genome. In the absence of any off-target mutations, which is evident from deep targeted sequencing in the potato experiment (Woo et al., 2015), genome-editing reagents[4] that do not leave a transgene in the genome would appear to be a valuable crop-breeding approach.

The above examples center on the use of SSNs to cleave DNA and introduce permanent changes in the sequence of the double-stranded DNA through either NHEJ or HDR. However, there are other applications by which proteins that bind to DNA in a sequence-specific manner can be exploited to modify genes and gene activity. They include fusion of the DNA-binding features of zinc finger proteins (ZFPs) or TALEs to activate domains to produce synthetic transcriptional activators. Without activator fusions, the ZFPs or TALEs can be used as transcriptional repressors. The design features of ZFPs and TALEs enable the production of synthetic transcription factors (TFs) to regulate the expression of practically any target gene (Figure 7-3). Indeed, TALE-TFs have been used in tandem to produce additive gene activation in transgenic plants (Liu et al., 2014). For the CRISPR/Cas9 system, a suite of molecules can be fused with a catalytically inactive Cas9 nuclease (dCas9) to permit a wide array of modifications of gene regulation, collectively known as CRISPR interference (reviewed in Doudna and Charpentier, 2014; Figure 7-3). Perhaps the simplest application is fusion of the dCas9 to a transcriptional activator or a transcriptional repressor; when introduced into a cell with a guide RNA, the transcriptional activator or repressor can modify the number of transcripts

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[4] Nucleases that have been customized to target a specific sequence are referred to as reagents.

of the target gene in a way similar to ZFPs and TALEs. The dCas9 genes could potentially be fused with chromatin modification genes and guided to a target region by the guide RNA to modify the epigenetic state of a locus and thereby affect transcription (Doudna and Charpentier, 2014).

> **FINDING: Exploitation of inherent biological processes—DNA binding-zinc finger proteins (ZFNs), pathogen-directed transcription of host genes (TALEs), and targeted degradation of DNA sequences (CRISPR/Cas)—now permit precise and versatile manipulation of DNA in plants.**

Artificial and Synthetic Chromosomes

Increased knowledge of biological processes and advanced molecular-biology tools will not only facilitate the engineering of multiple genes into plants but will also make possible the insertion of complete and novel biochemical pathways or processes. DNA constructs used in plant genetic engineering have been small (less than 20–40 kilobases) and have used traditional molecular cloning techniques that are slow and laborious. However, new and inexpensive methods of synthesizing DNA molecules and assembling them into larger DNA molecules have been developed. The methods permit rapid, easy construction of multigene pathways on a single DNA molecule (for review, see Ellis et al., 2011). The feasibility of the techniques has been demonstrated by the synthesis of an entire bacterial genome (Gibson et al., 2010) and the creation of a synthetic yeast chromosome (Annaluru et al., 2014). Researchers would like to be able to introduce tens to hundreds of genes into plants. One method envisaged to accomplish such advances would be the use of artificial minichromosomes or synthetic chromosomes. An artificial minichromosome is a chromosome added into the plant's natural composite of chromosomes in the nucleus. A synthetic chromosome (Annaluru et al., 2014) is a total synthesis of DNA to replace a natural chromosome or even an entire organelle genome, such as the plastome genome.

Artificial or synthetic chromosomes and genomes would allow the assembly of a large number of genes in a self-replicating molecule. In eukaryotes, chromosomes are linear DNA molecules with the proper sequences for replication (origins of replication), integrity (telomeres), and segregation in dividing cells (centromeres). The use of artificial or synthetic chromosomes would permit the introduction of genes into plants in a manner that does not have the potential to disrupt genes on native plant chromosomes at the sites of insertion.

No synthetic chromosomes or genomes have been created in plants, but the methods used to make a yeast synthetic chromosome (Annaluru et

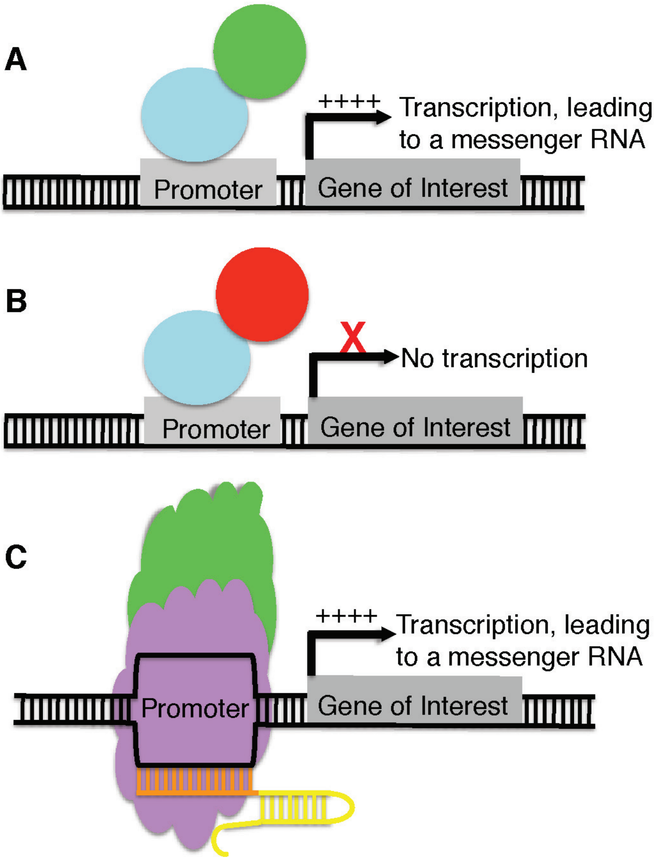

FIGURE 7-3 Alternative uses of genome-editing technologies.
SOURCE: Illustration provided by C. R. Buell.
NOTE: A, A zinc finger or transcription activator-like effector (TALE) (blue) can be fused to a transcriptional activator (green) to increase transcription of a gene of interest. B, A zinc finger or TALE (blue) can be fused to a transcriptional repressor (red) to suppress transcription of a gene of interest. C, A catalytically inactive Cas9 nuclease (purple) can be fused to a transcriptional activator (green) and, in the presence of a guide RNA (orange and yellow), guide the complex to the promoter of a gene of interest and increase transcription of the target gene. D, A catalytically

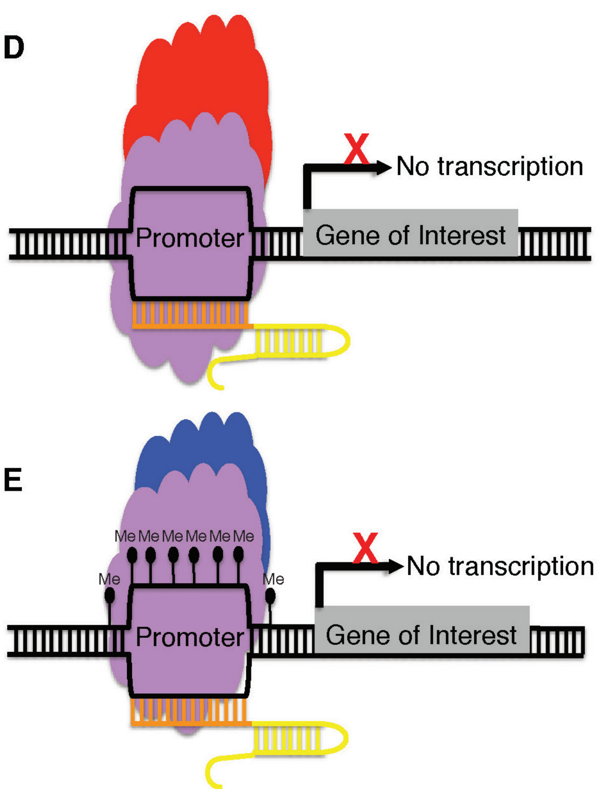

FIGURE 7-3 Continued

inactive Cas9 nuclease (purple) can be fused to a transcriptional repressor (red) and, in the presence of a guide RNA (orange and yellow), guide the complex to the promoter of a gene of interest and decrease transcription of the target gene. E, A catalytically inactive Cas9 nuclease (purple) can be fused to a DNA-methylating enzyme and, in the presence of a guide RNA (orange and yellow), guide the complex to the promoter of a gene of interest, targeting that gene for methylation and, as a consequence, suppressing transcription.

al., 2014) should be transferrable to plants. Yeast chromosome III, which is 316,617 bases, was replaced with a laboratory-synthesized chromosome of 272,871 bases. The chloroplast genome, which is one-half to one-third the size of yeast chromosome III, could foreseeably be synthesized and inserted into a plant, such as tobacco, that is already amenable to plastome transformation. The cost of DNA synthesis continues to decrease, so experimental development in this field would be economically feasible.

Research on artificial minichromosomes for plants has generally taken two approaches (reviewed in Gaeta et al., 2012; Birchler, 2015). In the "bottom-up" approach, the key parts of a chromosome—such as the centromere, telomere, origin of replication, and genes of interest—are assembled, and this results in a de novo minichromosome. Although progress has been made with this approach, additional characteristics, such as epigenetic modification of DNA nucleotides, can affect gene expression (see below) and the ability of the minichromosome to be replicated in a cell and have prevented the approach from being used routinely. The "top-down" approach essentially uses existing chromosomes—approximating the synthetic yeast chromosome approach—to build an artificial chromosome with an existing template. This approach has resulted in transmission of the minichromosome through meiosis but not as efficiently as that of native chromosomes. Neither approach has resulted in practically deployable minichromosomes. Thus, the use of a synthetic approach to replace DNA systematically, analogous to the approach in the yeast project, might be possible in the future (Birchler, 2015). It might also be possible that current bottom-up or top-down approaches could work in clonally propagated crops, such as potato, given that meiosis is not required (Birchler, 2015).

With a robust knowledge base of genes underlying plant biochemistry, precise constructs can be synthesized in vitro and introduced into a heterologous species through *Agrobacterium*-mediated or gene gun-mediated transformation or nuclease-targeted insertion at a single selected site. For example, sweet wormwood (*Artemisia annua*) produces artemisinin, an antimalarial compound. With five genes from yeast and from *A. annua*, tobacco was engineered to synthesize artemisinin (Farhi et al., 2011). Although the yield of artemisinin in tobacco was lower than that in *A. annua*, this proof-of-concept study demonstrated the feasibility of engineering heterologous biosynthetic pathways in plants. With further refinement of promoters, improved understanding of metabolite compartmentalization and transport and flux in cells and tissues, and development of such vectors as artificial chromosomes capable of transferring large segments of DNA to plant cells, genetic engineering of plants for complex traits, such as heterologous or novel biochemical pathways, and for specialized physiological and developmental processes, such as C4 photosynthesis, may be possible (see Chapter 8 for detail).

Targeted Epigenetic Modifications

As outlined earlier in this chapter, relatively stable, heritable changes in the expression of specific genes can result from changes in the epigenome. Changes in the methylation of DNA in particular are most likely to result in heritable changes in gene expression in plants. As the understanding of the biochemistry of the systems that change DNA methylation patterns increases, the ability to target specific genes for epigenetic modifications also increases. Such targeting would involve expressing the proteins and perhaps also specific nucleic acids (for example, a guide RNA) that would direct DNA methylation to a specific locus. The targeting system could be removed after the epigenetic modification is accomplished—for example, by using conventional plant breeding to segregate the targeting system.

On the key issue of safety, changing the epigenetic modifications of particular plant genes presents no fundamental problems; the genomes of plants are replete with epigenetic modifications, and epigenetically modified DNA has been in the environment and consumed by humans for thousands of years. Thus, the safety issue is the same as that involved in any technique, whether genetic engineering or non-genetic engineering, that results in an increase or decrease in the expression of specific genes in a plant and in specific trait alterations.

It should be noted that, in addition to targeted approaches, there are several ways to broadly and randomly alter the epigenome of a plant, such as overexpression of an enzyme that alters DNA methylation. Of course, broad and random approaches to altering a plant genome are not new: mutagenesis is a broad and random approach to genome modification. The utility of broad and random approaches to genome or epigenome modification is that if the biochemistry or genetics of a process is not sufficiently understood to permit a targeted approach—whether a genetic-engineering or a non–genetic-engineering approach (such as marker-assisted breeding)—a random approach might produce a desirable result. As discussed above, broad and random approaches will result in more unknown changes than targeted approaches.

Consistency is typically a desirable feature of new plant varieties. Given that epigenetic changes can revert to the initial state at varied frequencies, epigenetic modification might not be an ideal approach to produce new plant varieties. However, if a new plant variety derived from an epigenetic change is superior to stable alternatives, the potential for some degree of reversion may not be an obstacle to commercialization.

FUTURE APPLICATIONS OF GENOME EDITING

Of the emerging genetic-engineering technologies reviewed above, genome editing is the closest to being used to modify commercially available crops. A key component of effective and efficient application of genome editing is understanding the biochemical, molecular, and physiological basis of agronomic traits such as plant architecture, photosynthesis, pathogen resistance, and stress tolerance. Given advances in knowledge, additional genome-editing targets will emerge, and they will probably involve the manipulation of multiple genes (see Chapter 8). The committee also expects advances in the ability to edit plant genes precisely—that is, to make precise changes in specific genes without disrupting other genes. Such advances often come from basic research, whose far-reaching applications are not anticipated. For example, TALENs resulted from a study of how some plant-pathogenic *Xanthomonas* species modify gene expression in host plant cells. The CRISPR/Cas9 system resulted from the surprising discovery that some bacteria have an adaptable "immune system" to resist infection by viruses. The TALEN and CRISPR/Cas9 systems ushered in rapid advances in not only the ease but the range of genome-editing possibilities. In this section, the committee provides an overview of some of the expected applications of this transformation technology.

Removal of Genome-Editing Reagents in Genetically Engineered Crops

It is envisioned that genome editing will be useful in most agricultural crops in generating modified alleles that are homozygous in the modified line for several reasons: to prevent segregation of the altered allele in derived progeny, to eliminate the production of the wild-type target mRNA and protein, and to increase the dosage of the modified allele as the level of transcript of a gene is correlated with numbers of alleles. As described earlier, DNA-free genome editing via CRISPR is possible (Woo et al., 2015). With TALEN and CRISPR/Cas9 reagents, both heterozygous and homozygous mutations can be generated in the first transformed generation. Simple molecular-biology screens can be performed to identify individuals homozygous for the modified allele. Alternatively, for sexually reproducing self-compatible species, individual heterozygous transformed plants can be crossed with their own pollen and homozygous progeny identified in the second transformed generation. An important consideration when generating some genome-edited plants is to ensure that the reagent (TALEN, Cas9) is not present in the selected progeny; additional mutations can be generated if the reagents remain active. In some situations, the continued presence of the reagent is desirable. For example, the retained editing reagents can act as a constant mutagen and generate various modified alleles if sufficient gene family members that could be substrates for the reagents are present. However, that might not be desirable in an agronomic situation as stability of genetic material is essential for commercial production. Another example in which the continued presence of the reagent is necessary is gene-drive applications.

Gene Drive

In natural populations, genome-editing reagents can be used to create a gene-drive system, in which the frequency of a specific allele in the population is altered, affecting the likelihood that the desired allele will be inherited. A gene-drive system can be created by retaining the genome-editing reagents in the transgenic organism to enable continued editing of the target alleles throughout the population when the reagents are incorporated into the germline and passed to other members of the population through sexual reproduction; the use of CRISPR/Cas9 to create such a genome-editing system has been referred to as mutagenic chain reaction (Gantz and Bier, 2015). Gene drive has applications in the control of insect pests, such as mosquitoes, and various pests in crops (Esvelt et al, 2014). Inadvertent creation of a CRISPR/Cas9 gene-drive system can be avoided by ensuring that the gene constructs that encode the two cassettes[5] for Cas9 and the guide RNAs are not present in the GE plant that is developed. There are many ways to ensure this (Akbari et al., 2015). One way is to genetically segregate away the constructs after editing occurs. Another way is to employ DNA-free or transgene-free genome editing (Woo et al., 2015) in which only proteins and RNAs are introduced into the plant to accomplish gene editing.

Traits Involving Gain versus Loss of Function

Most commercialized GE crops have gain-of-function traits, such as herbicide resistance or insect resistance. Only recently have loss-of-function traits been readied for commercial sale in GE crops. An example is the nonbrowning apple (see Chapters 3 and 8). Chapter 8 describes a number of complex traits that were in the research stage when the committee was writing its report; many of them (such as water-use efficiency, nitrogen fixation, and enhanced carbon-fixation efficiency) exhibit gain of function, or perhaps a combination of gain of function with loss of function, and will probably involve the introduction of multiple genes (Box 7-2).

Given the time and expense associated with the regulatory process, intellectual-property constraints, and consumer wariness (see Chapter 6),

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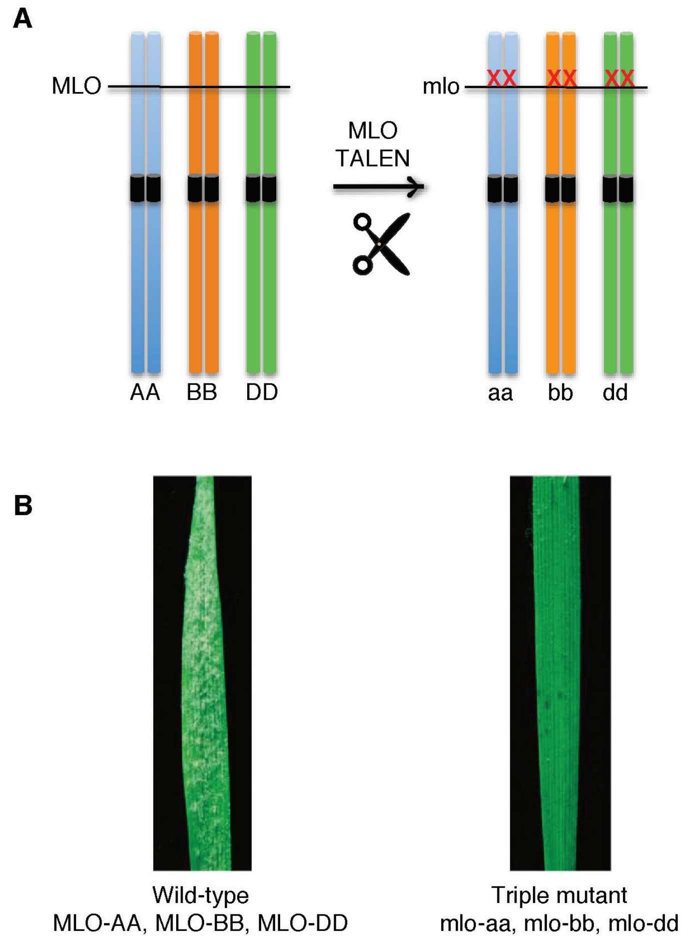
[5] A cassette is a DNA molecule that contains several genes that collectively function in a single process.

BOX 7-2
Disease-Resistant Wheat by Genome Editing

Bread wheat (*Triticum aestivum*) is a polyploid and contains three distinct genomes, which are termed A, B, and D. In each of the three genomes, a single dominant gene (*TaMLO-A1*, *TaMLO-B1*, or *TaMLO-D1*) confers susceptibility to the fungal powdery mildew pathogen *Blumeria graminis* f. sp. *tritici.* In barley (*Hordeum vulgare*), a close relative of bread wheat, the recessive allele of the orthologous locus (*Hvmlo)* confers resistance to the barley powdery mildew pathogen (Büschges et al., 1997). By using a pair of TALENs designed to target all three of the wheat MLO loci, NHEJ events were detected at each MLO locus that resulted in knockout mutations at all three loci (Wang et al., 2014; Figure 7-4). In regenerated plants in which all three MLO loci were mutated and homozygous (*tamlo-aabbdd*), resistance to *B. graminis* f. sp. *tritici* was observed. To demonstrate whether TALEN-mediated cleavage of the MLO loci could be used to edit the locus, a donor molecule encoding either the green fluorescent protein or a histidine-tagged protein was cotransformed along with the TALEN, resulting in integration of the donor molecule into the MLO locus. This type of modification is referred to as a “knock-in.” Preliminary work with a single CRISPR guide RNA targeted to *TaMLO-A1* yielded plants with mutations at this locus; this indicated the feasibility of achieving disease resistance in wheat with two distinct site-specific nuclease genome-editing technologies.



Wild-type
MLO-AA, MLO-BB, MLO-DD

Triple mutant
mlo-aa, mlo-bb, mlo-dd

FIGURE 7-4 An example of introducing a gain-of-function trait through two genome-editing approaches.

SOURCE: Illustration by C. R. Buell. Wheat image from Wang et al. (2014).

NOTE: A, the polyploid wheat genome encodes three dominant MLO genes that confer susceptibility to the fungal powdery mildew pathogen. Shown are each of the three MLO loci on homologous chromosomes, each homozygous for an MLO locus (MLO-AA, MLO-BB, MLO-DD). Transcription activator-like effector nucleases (TALENs) targeting the MLO genes were used to knockout all three MLO loci, which were then self-fertilized to generate homozygous knockout lines at all three loci (mlo-aa, mlo-bb, mlo-dd). B, wild-type wheat is susceptible to the wheat powdery mildew pathogen, but the triple mlo knockout is resistant.

some firms and organizations seek to develop desired traits without genetic-engineering approaches. Loss-of-function traits, particularly if only a single gene has to be disabled, can be readily obtained with the non-GE approach of mutagenesis because random changes in DNA sequence are more likely to disrupt than to improve protein function. At the other end of the spectrum, traits that require introduction of novel genes, or perhaps complex redirecting of gene expression to different tissue or cell types, may be achievable only with genetic-engineering approaches.

Consider the following theoretical example that aims to reduce the concentration of a toxic compound in the leaves of a potentially new crop plant. All available germplasm of the plant contains the toxic compound at unacceptable concentrations. Proof-of-concept studies might first explore the efficacy of downregulating the target gene responsible for synthesis of the toxic compound by using RNAi or knocking it out via CRISPR/Cas 9 or TALENs. Once the target is identified, an approach that does not involve genetic engineering, such as targeting induced local lesions in genomes (TILLING), could be applied. TILLING relies on initial chemical mutagenesis of a plant population followed by molecular identification of the required mutant allele and then crossing to obtain plants homozygous in that allele (Henikoff et al., 2004). It does not require the target plant to be genetically transformable. Although setting up the initial mutant TILLING population is expensive and fixing the required allele can be complex in polyploid outcrossing species, the approach can be cost-effective if multiple traits are being sought in the same species. TILLING populations have been available for several years for many crop and model species (Perry et al., 2003; Comis, 2005; Weil, 2009) and are being used in agricultural biotechnology (Comis, 2005; Slade and Knauf, 2005). However, it is not clear that traits produced by TILLING would pose less risk of unintended effects to the environment or food safety than those introduced by genetic-engineering approaches, such as RNAi and genome editing. The chemical mutagenesis used in TILLING introduces random mutations into the plant genome; although most of the mutations can be removed by backcrossing in most crop species, the resulting modified crop plant might have more unknown changes than the same change in the target gene of interest brought about by use of CRISPR/Cas 9 (although somaclonal variation will not be an issue because TILLING does not require a tissue-culture step).

There are both conventional-breeding and genetic-engineering approaches for the selection of gain-of-function traits such as increasing the amount of a beneficial component (for example, a nutrient or useful pharmaceutical compound). If sufficient natural variation is present in the species, breeding for increased production can be advanced by using marker-based or genomics-based approaches and development of an improved variety through marker-assisted introgression. A good example of this approach is the increase in production of the antimalarial compound artemisinin in wormwood (Graham et al., 2010). If natural variation is not present, as is the case in trying to introduce condensed tannins in foliage to improve forage quality in alfalfa (Lees, 1992), a genetic-engineering approach may be the only option available. Theoretically, it may be possible to introduce a gain-of-function trait through TILLING; if not, the trait can be introduced by overexpression of a key, rate-limiting biosynthetic enzyme or one or more positively regulating transcription factors. Examples of these approaches are presented in Chapter 8.

Editing Quantitative Trait Loci

Not every trait is governed by a single gene. Many agronomic traits are complex traits and are governed by multiple genetic loci that contribute to overall variation in the phenotype; the multiple genes involved in complex traits are known as quantitative trait loci (QTL). Scientists have identified a number of QTL for diverse agronomic and quality traits of a wide array of crop species. On the basis of high rates of coinheritance (linkage) with specific DNA sequences, specific progeny can be selected from conventional breeding to create combinations of QTL that are expected to perform well. They can be tested by field experimentation.

The use of QTL selection has limitations and impediments. First, for a number of crop species, backcrossing is difficult or impossible because of low sexual fertility, long reproduction cycles, inbreeding depression, or some combination thereof. Second, desirable QTL may be closely linked (coinherited) with genes that adversely affect other important traits, that is, “linkage drag;” this is common among genes in low-recombination regions of chromosomes and when desirable QTL are found in wild crop relatives whose genomes are less prone to recombination with the crop genome. Third, considerable effort is required to introgress a specific QTL into all plants of interest. Multiple backcrosses must be made to remove unlinked introgression events, which is expensive in terms of growing populations in the greenhouse or field for multiple generations. Thus, genome editing of QTL provides an alternative approach for developing elite varieties in species whose breeding cycles pose logistical challenges.

In the event that the specific nucleotides that govern a QTL are known, genome editing could be used to modify nucleotides in the QTL to the favorable alleles. Not all QTL have been defined at the gene or allele level; for most QTL, only a localized region of the genome has been defined as the QTL. Therefore, a region of the genome might be replaced by using genome-editing technologies, although current methods are inefficient and the restrictions on the length of DNA that can be edited are not yet known.

FINDING: Genome-editing methods can complement and extend contemporary methods of genetic improvement by modifying composition and expression of genes and by targeting insertion events.

FINDING: Current genome-editing methods and reagents are improving rapidly in precision and efficiency.

EMERGING TECHNOLOGIES TO ASSESS GENOME-EDITING SPECIFICITY

A highly touted feature of emerging genome-editing methods is their extreme specificity—ZFNs, TALENs, and the CRISPR/Cas9 nuclease system rely on recognition of a target sequence, so a single nucleotide in a genome can be targeted and modified. However, the extent of off-target effects is not well established, and off-target effects would potentially have unintended effects. The development of tools to assess such effects is important, and some emerging approaches are described below.

In Silico Prediction Methods

For ZFNs, TALENs, and CRISPR, computational programs have been developed that facilitate design of reagents to minimize off-target effects (for example, Fine et al., 2014; Heigwer et al., 2014; Naito et al., 2014). In general, the programs are tailored for each genome-editing reagent. The programs assess the homology of the target sequence to other sites in the genome; to address technical limitations or preferences such as nuclease specificity, binding energy, binding preferences, and maximal permitted mismatches, the user can modify various search parameters. As empirical data on off-target effects of genome-editing reagents accumulate (see below), the programs can be refined to improve their sensitivity and specificity.

Molecular-Based Methods

Multiple methods have been used to assess off-target effects of genome-editing reagents, from targeted amplification and assessment of one or a few candidate off-target loci to an unbiased approach in which all possible off-target effects are captured and examined by whole-genome DNA resequencing. For a few potential off-target loci, simple molecular-biology techniques can be used in which the locus is amplified and treated with a mismatch-specific nuclease that recognizes SNPs or insertions and deletions in heteroduplex DNA, and the products are then separated with gel electrophoresis. Alternatively, the polymerase chain reaction product can be sequenced and examined through sequence alignments. This inexpensive, rapid method is sufficient for small numbers of loci but is not scalable and is limited in requiring a priori knowledge of candidate off-target loci. Recently developed unbiased approaches include detection of double-strand breaks through the capture of synthesized double-stranded oligonucleotides, which is then coupled with high-throughput sequencing. This technique—termed genome-wide, unbiased identification of double-strand breaks enabled by sequencing (GUIDE-seq)—was recently demonstrated in human cell lines with the CRISPR/Cas9 genome-editing platform (Tsai et al., 2015). The GUIDE-seq experiment was able to identify a substantially higher number of off-target loci for 13 different CRISPR RNA-guided nucleases than predicted through computational off-target prediction programs. Indeed, although the GUIDE-seq method captured all known, predicted off-target loci, most of them were not detected computationally, and this suggests substantial sensitivity limitations in off-target prediction software. The GUIDE-seq method detected double-strand breaks that were independent of the CRISPR RNA-guided nucleases, so there may be inherent breakage of chromosomes independent of the genome-editing reagent. What was most notable about the Tsai et al. study was that a substantial reduction in off-target effects was observed by using truncated guide RNAs; this suggests that improvements in the design of the CRISPR reagents have strong potential to affect the specificity of genome editing. The GUIDE-seq method could readily be applied to plants for testing and optimizing genome-editing reagents in protoplasts before construction of an engineered, regenerated plant.

DETECTION OF GENOME ALTERATIONS VIA -OMICS TECHNOLOGIES

In the last 15 years, various advanced technologies have been developed that permit accumulation and assessment of large-scale datasets of biological molecules, including DNA sequence (the genome), transcripts (the transcriptome; involving RNA), DNA modification (the epigenome), and, to lesser extents, proteins and their modifications (the proteome) and metabolites (the metabolome). Such datasets enable comparative analyses of non-GE and GE lines in such a way that effects on plant gene expression, metabolism, and composition can be assessed in a more informed manner. Access to the technologies also permits analysis of the extent of the natural variation in a crop species at the DNA, RNA, protein, metabolite, and epigenetic levels, enabling determination of whether variation in GE crops is within the range found naturally and among cultivars. As discussed below for each of the -omics data types, technologies to access the molecules were relatively recent as of 2015 but were advancing rapidly. Some technologies were ready to be deployed to generate datasets for assessment of the effects of genetic-engineering events when the committee's report was being written. Others will improve in precision and throughput in the coming decade and may someday be useful technologies for assessing effects of genetic-engineering events. The Precision Medicine Initiative announced by President Obama in January 2015[6] focuses on understanding how genetic differences between individuals and mutations present in cancer and diseased cells (versus healthy cells) affect human health. An analogous project that uses diverse -omics approaches in crop plants with genetic engineering and conventional breeding could provide in-depth improvements in the understanding of plant biological processes that in turn could be applied to assessing the effects of genetic modifications in crop plants.

Genomics

One way to ascertain whether genetic engineering has resulted in off-target effects (whether through nuclear transformation with *Agrobacterium* or gene guns, RNAi, or such emerging technologies as genome editing) is to compare the genome of the GE plant with an example—or reference—genome of the parent non-GE plant. The reference genome is like a blueprint for the species, revealing allelic diversity and identifying the genes associated with phenotype. Knowing the variation that occurs naturally in a species, one can compare the engineered genome with the reference genome to reveal whether genetic engineering has caused any changes—expected or unintended—and to gain context for assessing whether changes might have adverse effects. Because there is inherent DNA-sequence variation among plants within a species, and even between cultivars, any genetically engineered changes would need to be compared to the non-GE parent and the range of natural genomic variation. That is, changes made by genetic engineering must be placed in an appropriate context.

Background

In July 1995, the first genome sequence of a living organism, the bacterium *Haemophilus influenza* (1,830,137 base pairs), was reported (Fleischmann et al., 1995). This paradigm-changing technological achievement was possible because of the development of automated DNA-sequencing methods, improved computer-processing power, and the development of algorithms for reconstructing a full genome on the basis of fragmented, random DNA sequences. In October 1995, the genome of the

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[6] Fact Sheet: President Obama's Precision Medicine Initiative. Available at https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative. Accessed November 12, 2015.

bacterium *Mycoplasma genitalium* was released (Fraser et al., 1995); this solidified whole-genome shotgun sequencing and assembly as the method for obtaining genome sequences. In the next two decades, higher throughput and less expensive methods for genome sequencing and assembly emerged (for review, see McPherson, 2014) and enabled the sequencing of the genomes of hundreds of species, as well as thousands of individuals, in all kingdoms of life. For example, since the release of the draft sequence of the human reference genome in 2001 (Lander et al., 2001; Venter et al., 2001), thousands of individual human genomes have been sequenced, including such comparative genome-sequencing projects as: a deep catalog of human variation of thousands of individuals,[7] normal versus tumor cells from a single individual, families with inherited genetic disorders, and diseased versus healthy populations. Those projects have focused on detecting the allelic diversity in a species and associating genes with phenotypes, such as the propensity for specific diseases.

Limitations in Current De Novo Genome Sequencing and Assembly Methods for Plants

Current methods to sequence a genome and assemble a genome de novo entail random fragmentation of DNA, generation of sequence reads, and reconstruction of the original genome sequence by using assembly algorithms. Although the methods are robust and continue to improve, it is important to note that they fail to deliver the full genome sequence of complex eukaryotes. Indeed, even the human genome sequence—for which billions of dollars have been spent to obtain a high-quality reference genome sequence that has provided a wealth of useful information in understanding of human biology, including cancer and other diseases—is still incomplete. For plants, the benchmark for a high-quality genome assembly is that of the model species *Arabidopsis thaliana*, which has an extremely small genome that was published in 2000 (*Arabidopsis* Genome Initiative, 2000). More than 15 years after the release of the *A. thaliana* reference genome sequence and with the availability of sequences from more than 800 additional accessions,[8] an estimated 30–40 million nucleotides of sequence were still missing from the *A. thaliana* Col-0 reference genome assembly (Bennett et al., 2003). Most of the missing sequences are highly repetitive (such as ribosomal RNA genes and centromeric repeats), but some gene-containing regions are absent because of technical challenges.

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[7] 1000 Genomes: A Deep Catalog of Human Genetic Variation. Available at http://www.1000genomes.org/. Accessed November 12, 2015.

[8] 1001 Genomes: A Catalog of *Arabidopsis thaliana* Genetic Variation. Available at http://1001genomes.org/. Accessed November 12, 2015.

With increased genome size and repetitive-sequence complexity, complete representation of the genome sequence becomes more challenging. Indeed, the genome assemblies of most major crop species (maize, wheat, barley, and potato) are all of only draft quality and have substantial gaps (Schnable et al., 2009; Potato Genome Sequencing Consortium, 2011; International Barley Genome Sequencing, 2012; Li et al., 2014a); none provides a complete, full representation of the genome.

In several major crops, when the committee was writing its report, projects equivalent to the human 10,000-genomes project were under way to determine the overall diversity of the species by documenting the "pan-genome" (Weigel and Mott, 2009). It has been surprising in several of these studies that there is substantial genomic diversity in some plant species not only in allelic composition but also in gene content (Lai et al., 2010; Hirsch et al., 2014; Li et al., 2014b). Thus, a single "reference" genome sequence derived from a single individual of a species will fail to represent the genetic composition and diversity of the overall population adequately and will therefore limit interpretations of directed changes in the genome (such as ones that can be delivered by emerging genome-editing methods that are being used to generate GE crops).

Resequencing: Assessing Differences Between the Reference and Query Genome

Once the DNA sequence of a crop's genome is assembled well enough to serve as a reference genome, resequencing becomes a powerful and cost-effective method for detecting genomic differences among related accessions (individuals) or GE lines. Resequencing entails generating random-sequence reads of the query genome (the genome that is being compared with the reference genome), aligning those sequence reads with a reference genome, and using algorithms to determine differences between the query and the reference. The strengths of this approach are that it is inexpensive and permits many query genomes to be compared with the reference genome and thereby provides substantial data about similarities and differences between individuals in a species (Figure 7-5). However, limitations of the approach can affect determination of whether two genomes are different. First, sequence read quality will affect data interpretation in that read errors can be misinterpreted as sequence polymorphisms. Second, the coverage of sequence reads generated can limit interrogation of the whole genome because the sampling is random and some regions of the genome are underrepresented in the read pool. Third, library construction[9] and sequencing

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[9] A library of DNA sequence is made by generating random fragments of the genome that collectively represent the full sequence of the genome.

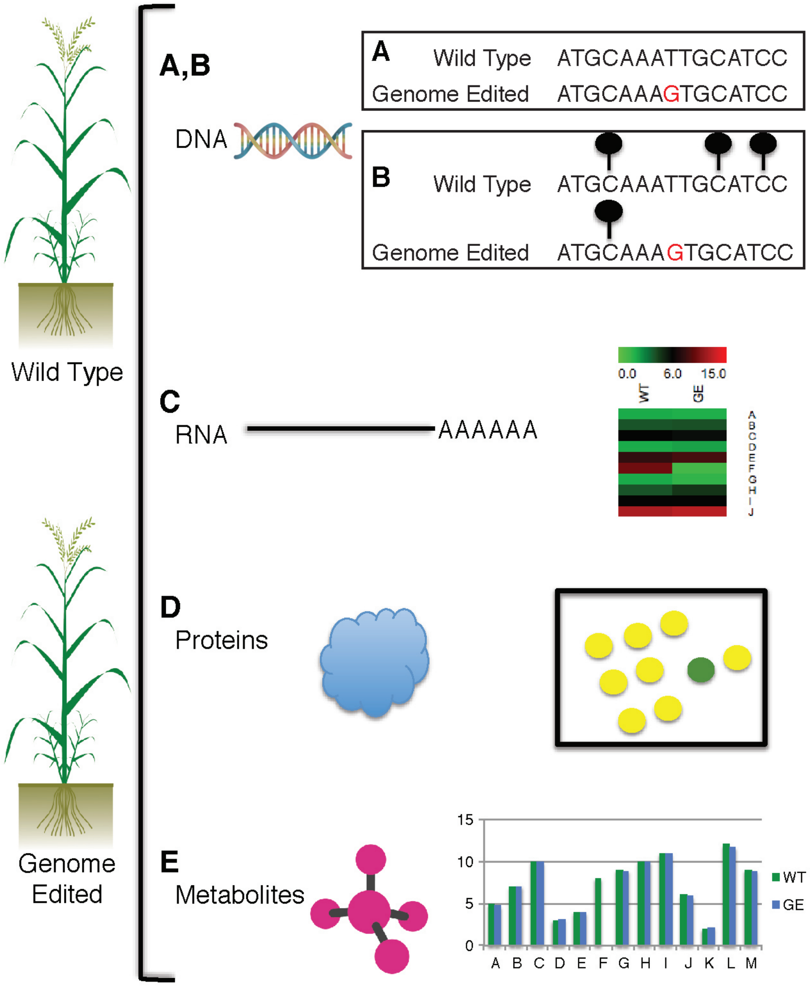

FIGURE 7-5 Detection of genome, epigenome, transcriptome, proteome, and metabolome alterations in genome-edited, genetically engineered plants.
SOURCE: Illustration by C. R. Buell.
NOTE: To perform various -omics assessments of genome-edited plants, both the wild-type (unmodified) and the genome-edited plant are subjected to genome sequencing, epigenomic characterization, transcriptome profiling, proteome profiling, and metabolite profiling. A, genome sequencing is performed on both the wild-type and genome-edited accession, and differences in the DNA sequence (red G) are detected with bioinformatics methods. B, changes in the epigenome are assessed with bisulfite sequencing and chromatin immunoprecipitation with

caption continues

bias will affect which sequences are present in the resequencing dataset and consequently available for alignment with the reference genome. Fourth, read-alignment algorithms fail to detect all polymorphisms if the query diverges too widely from the reference, especially with insertions and deletions or with SNPs near them. Fifth, read alignments and polymorphism detection are limited to nonrepetitive regions of the genome, so regions that are repetitive in the genome cannot be assessed for divergence. Although obstacles remain, resequencing is a powerful method for measuring differences in genome sequences between wild-type plants (normal untransformed individuals) and engineered plants. With expected improvements in technology, the resolution of resequencing to reveal differences between two genomes will improve.

Computational Approaches

Alternatives to resequencing approaches to identify polymorphisms in DNA sequence between two genomes were emerging when the committee was writing its report. The foundation of computational approaches to identify polymorphisms is algorithms that perform k-mer counting (a k-mer is a unique nucleotide sequence of a given length) in which unique k-mers are identified in two read pools (for example, wild type and mutant) and k-mers that differ between the two samples are then computationally identified. Those k-mers are then further analyzed to identify the nature of the polymorphism (SNP versus insertion or deletion) and to associate the polymorphism with a gene and potential phenotype (Nordstrom et al., 2013; Moncunill et al., 2014). The sensitivity and specificity of such programs are comparable with or better than the current methods that detect SNPs and

FIGURE 7-5 Continued

antibodies that target modified histones that are associated with chromatin; lollipops signify methylated cytosine residues. C, transcriptome sequencing is used to measure expression abundances in wild-type (WT) and genome-edited (GE) lines; in example shown, expression ranges from 0 to 15 for genes A through J; variance in all the genes is apparent, with only gene F showing substantial expression differences between the wild-type and the genome-edited line as would be expected in a knockout line. D, proteomics is used to measure differences in protein abundance in wild-type vs genome-edited line; all proteins are equally present in wild-type and genome-edited lines (yellow dots), whereas protein F is present only in wild-type line (green dot), as expected from a knockout line. E, levels of metabolites A through M in wild-type and genome-edited lines; levels of metabolite F are zero in contrast to the wild type, as would be expected in a knockout line.

insertions/deletions by using genome-sequencing methods and thus have the potential to identify more robustly genome variation introduced through genetic engineering. The committee expects the field to continue to develop rapidly and to enable researchers to read genomic DNA with increased sensitivity and specificity.

Utility of Transcriptomics, Proteomics, and Metabolomics in Assessing Biological Effects of Genetic Engineering

As stated in the 2004 National Research Council report *Safety of Genetically Engineered Foods*, understanding the composition of food at the RNA, protein, and metabolite levels is critical for determining whether genetic engineering results in a difference in substantial equivalence compared to RNA, protein, and metabolite levels in conventionally bred crops (NRC, 2004; see Chapter 5). Although the genome provides the "blueprint" for the cell, assessment of the transcriptome, proteome, and metabolome can provide information on the downstream consequences of genome changes that lead to altered phenotype. Methods used to assess transcripts, proteins, and metabolites in plants are described below with the committee's commentary on limitations of the sensitivity and specificity of detection and interpretation that existed when this report was being written. One caveat in the use of any of these techniques is related to inherent biological variation regardless of genetic-engineering status. Even with identical genotypes grown under identical conditions, there is variation in the transcriptome, proteome, and metabolome. Scientists address such variation by using biologically replicated experiments and multiple -omics and molecular-biology approaches. In addition to biological variation, allelic variation results in different levels of transcripts, proteins, and metabolites in different accessions. To provide context to any observed changes in the transcriptome, proteome, or metabolome attributable to a genetic-engineering event, the broader range of variation in commercially grown cultivars of a crop species can be compared with that of a GE line to determine whether modified levels are outside the realm of variation in a crop. Thus, in assessment of GE crops, interpretation must be in the context of inherent biological and allelic variation of the specific crop. Assessment is also made difficult by the fact that scientists have little or no knowledge of what functions a substantial number of genes, transcripts, proteins, and metabolites perform in a plant cell.

Transcriptomics

Advancements in high-throughput sequencing technologies have enabled the development of robust methods for quantitatively measuring the transcriptome, the expressed genes in a sample. One method, known as RNA sequencing (RNA-seq), entails isolation of RNA, conversion of the RNA to DNA, generation of sequence reads, and bioinformatic analyses to assess expression levels, alternative splicing, and alternative transcriptional initiation or termination sites (Wang et al., 2009; de Klerk et al., 2014). This method can be applied to mRNA, small RNAs (which include interfering RNAs involved in RNAi), total RNA, RNA bound to ribosomes, and RNA-protein complexes to gain a detailed assessment of RNAs in a cell. Methods to construct RNA-seq libraries, generate sequence reads, align to a reference genome, and determine expression abundances are fairly robust even with draft genome sequences if they provide nearly complete representation of the genes in the genome (Wang et al., 2009; de Klerk et al., 2014). Statistical methods to determine differential expression between any two samples, such as two plants with identical genotypes at different developmental stages, are continuing to mature but are limited by inherent biological variation in the transcriptome. Indeed, variation between independent biological replicates of wild-type tissues is well documented. For example, estimation of whole-transcriptome expression abundance in independent biological replicates of a given experimental treatment is considered to be highly reproducible if Pearson's correlation values are more than 0.95; values greater than 0.98 are typically observed. However, even with high Pearson's correlation values, numerous genes may exhibit different expression among biological replicates. Thus, differential gene expression in GE plants would need to be compared with the observed variation in gene expression in biological replicates of untransformed individuals to ensure the absence of major effects of the genetic-engineering event on the transcriptome.

Overshadowing any expression differences discovered between a wild-type plant and an engineered plant is the fact that little is known about the exact function of a substantial number of genes, transcripts, and proteins for any plant species. In maize, nearly one-third of the genes have no meaningful functional annotation; even when informative functional annotation is provided, the annotation was most likely assigned by using automated transitive annotation methods that depend heavily on sequence similarity. Thus, even if differentially expressed genes are detected between the wild-type and GE samples, interpreting them in the context of health or effects on the ecosystem may be challenging at best. For example, a study of the effects of expression of the antifungal protein in rice that was introduced with genetic engineering showed changes in about 0.4 percent of the transcriptome in the GE lines (Montero et al., 2011). Analysis of 20 percent of the changes indicated that 35 percent of the unintended effects could be attributed to the tissue-culture process used for plant transformation and regeneration, whereas 15 percent appeared to be event-specific and attributable to the presence of the transgene. About 50 percent of the changes that were attributed to the presence of the transgene were in expression of genes that could be induced in the non-GE rice by wounding. It is impossible to determine whether the changes in transcript levels recorded in the study indicate that the GE rice might be worse than, equal to, or better than its non-GE counterpart as regards food safety. One way to assess the biological effects of genetic engineering on the transcriptome is to include a variety of conventionally bred cultivars in the study and determine whether the range of expression levels in the GE line falls within the range observed for the crop, but this method will not provide definitive evidence of food or ecosystem safety.

Proteomics

Several methods permit comparison of protein composition and post-translational protein modifications between samples (for review, see May et al., 2011). For example, two-dimensional difference in-gel electrophoresis permits quantitative comparison of two proteomes through differential labeling of the samples followed by separation and quantification (Figure 7-5 D). In mass spectrometry (MS), another method for examining the proteome, proteins are first broken into specific fragments (often by proteases, which are enzymes that catalyze the cleavage of proteins into peptides at specific sites) and fractionated with such techniques as liquid chromatography. Then the mass-to-charge ratios of the peptides are detected with MS. MS data typically provide a unique "signature" for each peptide, and the identity of the peptides is typically determined by using search algorithms to compare the signatures with databases of predicted peptides and proteins derived from genome or transcriptome sequence data. Differential isotope labeling can be used in the MS approach to determine quantitative differences in protein samples. One limitation of all current proteomic techniques is sensitivity; whole-proteome studies typically detect only the most abundant proteins (Baerenfaller et al., 2008). Furthermore, sample-preparation methods need to be modified to detect different fractions of the proteome (such as soluble versus membrane-bound and small versus large proteins) (Baerenfaller et al., 2008). Thus, to provide a broad assessment of the proteome, an array of sample-preparation methods must be used. Finally, as with the other -omics methods, interpretation of the significance of proteomic differences is made difficult by the fact that scientists have little knowledge of what a large number of proteins do in a plant cell.

Metabolomics

It is common practice in evaluating GE crops for regulatory approval to require targeted profiling of specific metabolites or classes of metabolites that may be relevant to the trait being developed or that are known to be present in the target species and to be potentially toxic if present at excessive concentrations. Under current regulatory requirements, substantial metabolic equivalence is assessed on the basis of concentrations of gross macromolecules (for example, protein or fiber), such nutrients as amino acids and sugars, and specific secondary metabolites that might be predicted to cause concern.

As with genomics, transcriptomics, and proteomics, the approaches collectively known as metabolomics have been developed to determine the nature and concentrations of all metabolites in a particular organism or tissue. It has been argued that such information should be required before a GE crop clears regulatory requirements for commercialization. However, in contrast with genomic and transcriptomic approaches, with which it is now technically easy to assess DNA sequences and measure relative concentrations of most or all transcripts in an organism with current sequencing technologies respectively, metabolomics as currently performed can provide useful data only on a subset of metabolites. That is because each metabolite is chemically different, whereas DNA and RNA comprise different orderings of just four nucleotide bases. Metabolites have to be separated, usually with gas chromatography or high-performance liquid chromatography; their nature and concentrations are then determined, usually with MS. The mass spectra are compared with a standard library of chemicals run on the same analytical system. The major problem for this type of metabolomic analysis of plants is the possession in the plant kingdom of large numbers of genus-specific or even species-specific natural products (see section "Comparing Genetically Engineered Crops and Their Counterparts" in Chapter 5 for discussion of plant natural products). Advanced commercial platforms for plant metabolomics currently measure about 200 identified compounds, usually within primary metabolism, and less broadly distributed natural products are poorly represented (Clarke et al., 2013). However, these approaches can differentiate a much larger number of distinct but unidentified metabolites, and it is useful to know whether concentrations of a metabolite are specifically affected in a GE crop even if the identity of the particular metabolite is not known. For example, with a combination of separation platforms coupled to mass spectrometry, it was possible to resolve 175 unique identified metabolites and 1,460 peaks with no or imprecise metabolite annotation, together estimated to represent about 86 percent of the chemical diversity of tomato (*Solanum lycopersicum*) as listed in a publicly available database (Kusano et al., 2011). Although such an approach allows one to determine whether metabolite peaks are present in a GE crop but not in the non-GE counterpart or vice versa, metabolomics, in the absence of a completely defined metabolome for the target species in which the toxicity of all components is known, is not able to determine with confidence that a GE or non-GE plant does not contain any chemically identified molecule that is unexpected or toxic.

An alternative approach to nontargeted analysis of metabolites is to perform metabolic fingerprinting and rely on statistical tools to compare GE and non-GE materials. That does not necessarily require prior separation of metabolites and can use flow-injection electrospray ionization mass spectrometry (Enot et al., 2007) or nuclear magnetic resonance (NMR) spectroscopy (Baker et al., 2006; Ward and Beale, 2006; Kim et al., 2011). NMR spectroscopy is rapid and requires no separation but depends heavily on computational and statistical approaches to interpret spectra and evaluate differences.

Generally, with a few exceptions, metabolomic studies have concluded that the metabolomes of crop plants are affected more by environment than by genetics and that modification of plants with genetic engineering typically does not bring about off-target changes in the metabolome that would fall outside natural variation in the species. Baseline studies of the metabolomes (representing 156 metabolites in grain and 185 metabolites in forage) of 50 genetically diverse non-GE DuPont Pioneer commercial maize hybrids grown at six locations in North America revealed that the environment had a much greater effect on the metabolome (affecting 50 percent of the metabolites) than did the genetic background (affecting only 2 percent of the metabolites); the difference was more striking in forage samples than in grain samples (Asiago et al., 2012). Environmental factors were also shown to play a greater role than genetic engineering on the concentrations of most metabolites identified in *Bt* rice (Chang et al., 2012). In soybean, nontargeted metabolomics was used to demonstrate the dynamic ranges of 169 metabolites from the seeds of a large number of conventionally bred soybean lines representing the current commercial genetic diversity (Clarke et al., 2013). Wide variations in concentrations of individual metabolites were observed, but the metabolome of a GE line engineered to be resistant to the triketone herbicide mesotrione (which targets the carotenoid pathway that leads to photobleaching of sensitive plants) did not deviate with statistical significance from the natural variation in the current genetic diversity except in the expected changes in the targeted carotenoid pathway. Similar metabolomic approaches led to the conclusion that a Monsanto *Bt* maize was substantially equivalent to conventionally bred maize if grown under the same environmental conditions (Vaclavik et al., 2013) and that carotenoid-fortified GE rice was more similar to its parental line than to other rice varieties (Kim et al., 2013). Those studies suggest that use of metabolomics for assessing substantial equivalence will require testing in multiple locations and careful analysis to differentiate genetic from environmental effects, especially because there will probably be effects of gene–environment interactions.

Some metabolomic and transcriptomic studies have suggested that transgene insertion or the tissue-culture process involved in regeneration of transformed plants can lead to "metabolic signatures" associated with the process itself (Kusano et al., 2011; Montero et al., 2011). That was reported for GE tomatoes with overproduction of the taste-modifying protein miraculin, although it was pointed out by the authors that, as in comparable studies with other GE crops, "the differences between the transgenic lines and the control were small compared to the differences observed between ripening stages and traditional cultivars" (Kusano et al., 2011).

For metabolomics to become a useful tool for providing enhanced safety assessment of a specific GE crop, it will be necessary to develop a chemical library that contains all potential metabolites present in the species under all possible environmental conditions. It is a daunting task that may be feasible for a few major commodity crops under currently occurring biotic and abiotic stresses, but even that would not necessarily cover future environmental conditions. Annotated libraries of metabolites are unlikely to be developed for minor crops in the near future.

The Epigenome

Background

Whereas the DNA sequence of a gene encodes the mRNA that is translated into the corresponding protein, the rate at which a gene in the nucleus of a eukaryotic cell is transcribed into mRNA can be heavily influenced by chemical modification of the DNA of the gene and by chemical modification of the proteins associated with the DNA. In plants and other eukaryotes, genomic nuclear DNA can be chemically modified and is bound to an array of proteins in a DNA–protein complex termed chromatin. The major proteins in chromatin are histone proteins, which have an important role in regulating the accessibility of the transcriptional machinery to the gene and its promoter (regulatory region) and thereby control synthesis of mRNAs and proteins. Multiple types of histone proteins are found in plants, each with an array of post-translational modification (for example, acetylation and methylation) that can affect transcriptional competence of a gene. DNA can also be covalently modified by methylation of cytosines that affect transcriptional competence. Collectively, those modifications, which influence the expression of genes and are inheritable over various time spans, are known as epigenetic marks.

Epigenetic marks are determinants of transcriptional competence, and alteration of the epigenetic state (which occurs naturally but infrequently) can alter expression profiles or patterns of target genes. For example, when a transposable element inserts in or near a gene, the gene can be "silenced" as regions near a transposon become highly methylated and transcriptionally suppressed owing to the activity of the cell's native RNA-mediated DNA methylation machinery. Different epigenetic marks occur naturally in crop species; examples of transposable element-mediated gene silencing include allelic variation at the tomato 2-methyl-6-phytylquinol methyltransferase gene involved in vitamin E biosynthesis (Quadrana et al., 2014) and imprinting as seen in endosperm tissue, in which differential insertion of transposable elements occurs in the maternal and paternal parents (Gehring et al., 2009).

Methods of Characterizing the Epigenome

Methods of characterizing the epigenome are available and improving rapidly. For DNA methylation, high-throughput, single-nucleotide resolution can be obtained through bisulfite sequencing (BS-seq; for review, see Feng et al., 2011; Krueger et al., 2012). BS-seq methods mirror that of genome resequencing except that the genomic DNA is first treated with bisulfite, which converts cytosines to uracils but does not affect 5-methylcytosine residues. As a consequence, nonmethylated cytosines will be detected as thymidines after the polymerase chain reaction step during epigenome-library construction. After sequencing, reads are aligned with a reference genome sequence, and nonmethylated cytosines are detected as SNPs and compared with a parallel library constructed from untreated DNA (see section above "Resequencing: Assessing Differences Between the Reference and Query Genome"; Figure 7-5). There are limitations of BS-seq approaches, such as incomplete conversion of cytosines, degradation of DNA, and an inability to assess the full methylome because of read mapping limitations, sequencing depth, and sequencing errors, as described above for resequencing. Another limitation is the dynamic nature of plant genome cytosine methylation. Plants derived from an identical parent that have not been subject to any traditional selection or GE transformation can have different epigenomes—an example of "epigenetic drift" (Becker et al., 2011). Thus, determining the epigenome of a plant at one specific point in time will not necessarily indicate the future epigenome of offspring of that plant.

Histone marks can be detected through chromatin immunoprecipitation coupled with high-throughput sequencing (ChIP-Seq; for review see Yamaguchi et al., 2014; Zentner and Henikoff, 2014). First, chromatin is isolated so that the proteins remain bound to the DNA. Then the DNA is sheared, and the DNA that is bound to specific histone proteins is selectively removed by using antibodies specific to each histone mark. The DNA bound to an antibody is then used to construct a library that is sequenced and aligned with a reference genome, and an algorithm is used to define the regions of the genome in which the histone mark is found. Sensitivity and specificity of ChIP-Seq depend heavily on the specificity of the histone-mark antibodies, on technical limitations in alignment of sequence reads with the reference genome, and on the overall quality of the reference genome itself. Also, the present state of understanding does not permit robust prediction of the effects of many epigenetic modifications on gene expression, and gene expression can be more thoroughly and readily assessed by transcriptomics.

Evaluation of Crop Plants Using -Omics Technologies

The -omics evaluation methods described above hold great promise for assessment of new crop varieties, both GE and non-GE. In a tiered regulatory approach (see Chapter 9), -omics evaluation methods could play an important role in a rational regulatory framework. For example, consider the introduction of a previously approved GE trait such as a *Bt* protein in a new variety of the same species. Having an -omics profile in a new GE variety that is comparable to the profile of a variety already in use should be sufficient to establish substantial equivalence (Figure 7-6, Tier 1). Furthermore, -omics analyses that reveal a difference that is understood to have no adverse health effects (for example, increased carotenoid content) should be sufficient for substantial equivalence (Figure 7-6, Tier 2).

The approach described above could also be used across species. For example, once it is established that production of a protein (such as a *Bt* protein) in one plant species poses no health risk, then the only potential health risk of *Bt* expression in another species is unintended off-target effects. -Omics analyses that reveal no differences (Figure 7-6, Tier 1) or in which revealed differences present no adverse health effects (Figure 7-6, Tier 2) in comparison with the previously deregulated GE crop or the range of variation found in cultivated, non-GE varieties of the same species provide evidence for substantial equivalence. As discussed in Chapter 5 (see section "Newer Methods for Assessing Substantial Equivalence"), there have been more than 60 studies in which -omics approaches were used to compare GE and non-GE varieties, and none of these studies found differences that were cause for concern.

There are also scenarios for which -omics analyses could indicate that further safety testing is warranted, such as if -omics analyses reveal a difference that is understood to have potential adverse health effects (for example, increased expression of genes responsible for glycoalkaloid synthesis) (Figure 7-6, Tier 3). Another scenario is if -omics analyses reveal a change of a protein or metabolite for which the consequences cannot be interpreted and are outside the range observed in GE and non-GE varieties of the crop (Figure 7-6, Tier 4). It is important to note that a Tier 4 scenario is not in and of itself an indication of a safety issue. The functions

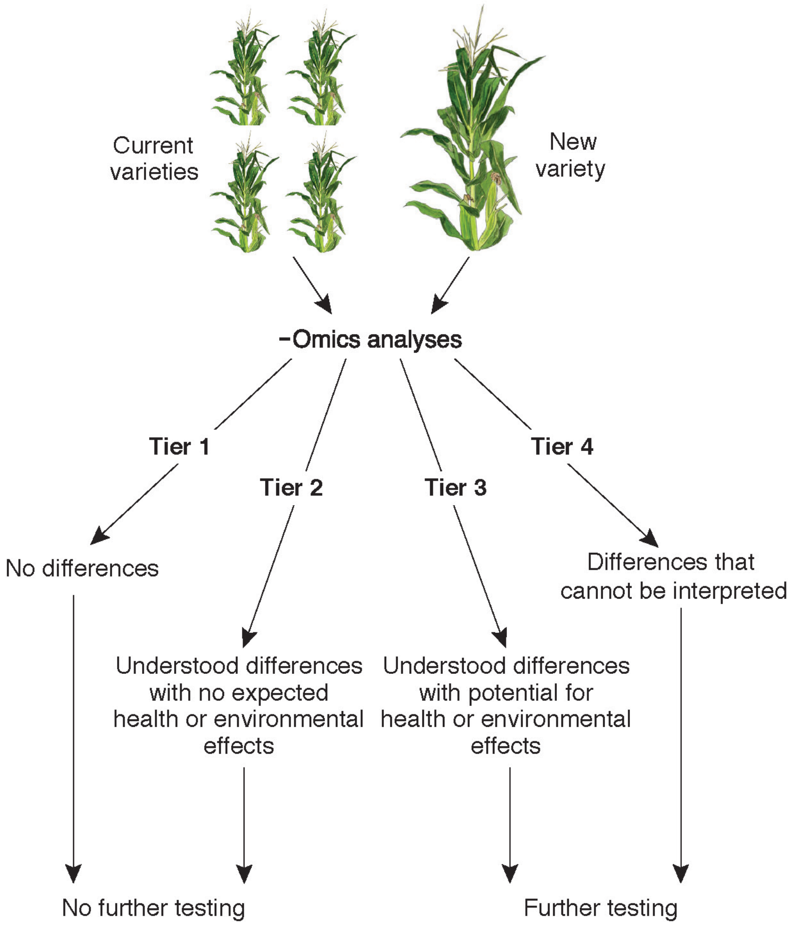

FIGURE 7-6 Proposed tiered crop evaluation strategy crops using -omics technologies.
SOURCE: Illustration by R. Amasino.
NOTE: A tiered set of paths can be taken depending on the outcome of the various -omics technologies. In Tier 1, there are no differences between the variety under consideration and a set of conventionally bred varieties that represent the range of genetic and phenotypic diversity in the species. In Tier 2, differences are detected that are well understood to have no expected adverse health or environmental effects. In Tiers 3 and 4, differences are detected that may have potential health or environmental effects and thus require further safety testing.

or health effects of consumption of many genes and corresponding RNAs, proteins, and metabolites in non-GE plants are not known. Furthermore, the chemical structure of many metabolites in plants that can be detected as "peaks" in various analytical systems is not known. Substantially more basic knowledge is needed before -omics datasets can be fully interpreted.

The state of the art of the different -omics approaches varies considerably. Advances in the efficiency of DNA-sequencing technology enable a complete genome or transcriptome to be sequenced at a cost that is modest on the scale of regulatory costs. Transcriptomics could play an important role in evaluation of substantial equivalence because it is relatively straightforward to generate and compare extensive transcriptomic data from multiple biological replicates of a new crop variety versus its already-in-use progenitor. As noted above, if no unexpected differences are found, this is evidence of substantial equivalence. It is possible that two varieties with equivalent transcriptomes have a difference in the level of a metabolite due to an effect of the product of a transgene on translation of a particular mRNA or on activity of a particular protein, but these are unlikely scenarios.

It is also straightforward and relatively low in cost to generate genome-sequence data from many individuals from a new GE or non-GE variety to determine which lineage has the fewest nontarget changes to its genome. As noted earlier in the chapter, mutagenesis, although currently classified as conventional breeding, can result in extensive changes to the genome; thus generating DNA sequence data will be useful in evaluating varieties produced by this method.

Metabolomic and proteomic techniques cannot presently provide a complete catalog of the metabolome or proteome. Nevertheless, these -omics approaches can play a role in assessment. For example, a similar metabolome or proteome in a new variety compared to an existing variety provides supporting evidence of substantial equivalence, whereas a difference can indicate that further evaluation may be warranted.

The most thorough evidence of substantial equivalence would result from a complete knowledge of the biochemical constituents of one crop variety compared to other varieties. As noted above, that is not possible with present techniques for the proteome and metabolome. However, looking to the future, an increasing knowledge base of plant biochemistry will translate into fewer analyses that result in a Tier 4 situation, and basic research in plant biochemistry will continue to expand the knowledge base that will enable the thorough and rational evaluation of new crop varieties; basic research will also expand fundamental understanding of basic biological processes in plants and thus enable advances in molecular plant breeding.

FINDING: Application of -omics technologies has the potential to reveal the extent of modifications of the genome, the transcriptome, the epigenome, the proteome, and the metabolome that are attributable to conventional breeding, somaclonal variation, and genetic engineering. Full realization of the potential of -omics technologies to assess substantial equivalence would require the development of extensive species-specific databases, such as the range of variation in the transcriptome, proteome, and metabolome in a number of genotypes grown in diverse environmental conditions. Although it is not yet technically feasible to develop extensive species-specific metabolome or proteome databases, genome sequencing and transcriptome characterization can be performed.

RECOMMENDATION: 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.

CONCLUSIONS

Modern plant breeding and genetic engineering are complementary methods for improving crop yield, production efficiency, and composition. Anti-sense and RNAi technologies offer capabilities that differ from simple transgene overexpression strategies. The emerging genetic-engineering technologies—such as genome editing and synthetic biology—when coupled with knowledge of the genetic basis of phenotypes enable construction of not only improved varieties of crops but crops with novel traits.

Both genetic engineering and conventional breeding have been greatly enhanced by increases in basic knowledge about plant biology and by technological innovations. Emerging genetic-engineering technologies have the potential to substantially change future crop production because of paradigm-shifting capabilities in precision, complexity, and diversity (see examples in Chapter 8). They have also developed markedly in ease of application and are poised to extend the range of individual improvements in crops—that is, endowing them with new traits (sometimes single traits but also multiple traits) and capabilities. Since the 1990s, there has been a revolution in DNA-sequencing technologies and associated technologies for detecting major molecules in cells, especially DNA and transcripts but also proteins, metabolites, and epigenetic marks. Plant breeders, geneticists, and other scientists have used -omics technologies to understand biological function better. The breadth of understanding has improved the efficiency of conventional plant breeding and increased scientists' ability to "read" DNA, which will be a harbinger of parallel developments in the ability to "write" DNA into organisms by using various advances in genome editing and synthetic biology. It is important that basic knowledge regarding biology continues to grow and that technology continues to improve.

In addition to contributing to crop improvement, emerging -omics methods could provide a rational pathway to developing a tiered approach for assessing health and environmental effects of new crop varieties produced by conventional breeding and genetic engineering.

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8

Future Genetically Engineered Crops

With a foundation in emerging genetic-engineering technologies provided in the preceding chapter, the purpose of this chapter is to offer a preliminary assessment of the potential to develop new traits and crops on the basis of the emerging technologies and evaluate how the traits themselves could affect agriculture and society. The committee also considers the social and economic forces that may foster or slow the development of these new traits and crops. The committee defines new traits as ones that have yet to be commercialized as of June 2015 even if the traits had received regulatory approval by that time or if there were published descriptions in the literature of the traits in crop plants.

As discussed in Chapter 3, few genetically engineered (GE) traits have been commercialized. They have mostly been incorporated into major commodity crops grown on millions of hectares worldwide. Many predicted GE traits are expected to be introduced into crops planted over smaller areas than the major commodities such as maize (*Zea mays*) and soybean (*Glycine max*). Some of those traits will be variations on GE traits that existed in 2015, such as resistance to new herbicides or the stacking of currently available traits. New and more diverse traits are also expected (Parisi et al., 2016).

It is not possible to predict with certainty the traits that will and will not make it to market or be diffused through nonmarket mechanisms in the future. The outcome will depend on environmental challenges that need to be addressed (for example, climate change), political–economic drivers, the regulatory landscape, and the rate of scientific advances, which is in part a function of the availability of public and private science funding. Genetic-engineering technologies have advanced rapidly, as outlined in Chapter 7, but the genetic basis of complex traits—such as drought tolerance (Yue et al., 2006), water-use efficiency (Easlon et al., 2014), and nitrogen-use efficiency (Rothstein et al., 2014)—is not fully understood. Only continued public funding of basic research will enable further advances in understanding of the physiological, biochemical, and molecular basis of these important traits. Furthermore, the potential for any of the new scientific insights and technologies to yield public benefits will depend on the social, political, and economic contexts in which they are generated and diffused.

IS GENETIC ENGINEERING NECESSARY TO DELIVER THE NEXT GENERATION OF PLANT TRAITS?

As noted in Chapter 7, new discoveries in molecular biology and genomics are offering novel tools for increasing the efficiency of both conventional plant breeding and genetic engineering of crops. The committee heard from invited speakers who concluded that the molecular approaches to conventional breeding were safer than and superior to genetic engineering and who raised the question of whether genetic engineering was necessary even to deliver useful new crop varieties (Cotter, 2014; Gurian-Sherman; 2014; Shand, 2014). It is the case for many crops that the genetic potential that exists in sexually compatible germplasm is quite large, and much crop improvement can be achieved by conventional breeding. However, conventional breeding, whether or not it incorporates such modern tools as marker-assisted selection (MAS; discussed in Chapter 7 section “Modern Plant-Breeding Methods”), is limited by the genetic potential in sexually compatible germplasm. Thus, conventional breeding could never achieve some traits, such as the incorporation of a natural insecticide from another species into a particular crop plant (for example, a Cry protein from *Bacillus thuringiensis*). As discussed in Chapter 4, progress in crop improvement has been brought about by the combined use of conventional breeding and genetic engineering. Furthermore, the committee finds that the distinction between conventional breeding and genetic engineering is becoming less obvious. For example, genome editing can now be used to make a trait-changing, single-nucleotide substitution in a specific gene, and the same nucleotide change can be made with the TILLING (targeting induced local lesions in genomes) method described in Chapter 7. The TILLING method would be considered conventional breeding within the context of most national regulatory systems because it uses radiation-induced or chemical-induced mutations linked with genomic screening to find and isolate the specific nucleotide change. These identical changes made by genome editing (genetic engineering) or TILLING (conventional breeding) would have the same effect on crop qualities or yield, and either could have unintended effects.[1]

Proponents of the argument that MAS can and should replace genetic engineering as a tool to deliver new traits (Vogel, 2009; Cotter, 2014) posit that more traits have been successfully introduced with MAS than with genetic engineering and that this approach is better suited to developing crop varieties with traits conducive to sustainable agricultural production (Cotter, 2014). As noted above, if the genetic potential for a trait of interest is present in sexually compatible germplasm, then conventional breeding with or without the efficiency provided by MAS could be used to introduce that trait. However, if the genetic potential is not present in sexually compatible germplasm, MAS will be of no value. For example, plant breeders have worked for decades to develop an alfalfa (*Medicago sativa*) that is "bloat-safe" for cattle. Such a variety would contain higher concentrations of condensed tannins to protect protein from being too rapidly metabolized by microorganisms in the cow's digestive tract (Lees, 1992; Coulman et al., 2000). However, despite years of plant-breeding efforts, alfalfa germplasm with sufficient tannin in vegetative tissues has not been obtained, and forage species that have naturally high levels of tannin in their leaves or stems are not sexually compatible with alfalfa. Therefore, on the basis of current knowledge, genetic engineering is still the only way to introduce this trait into alfalfa (Lees, 1992).

With an ever-increasing understanding of plant biology, commercial plant-breeding programs can now be armed with knowledge of the exact physical nature of the genes that need to be manipulated at the outset. Knowing the phenotypic effects of changing the expression of the target gene is critical for generating a desired trait. Such information can be obtained through the application of -omics technologies (discussed in Chapter 7) and could be of great value in both genetic engineering and conventional breeding of the trait, depending on which is most efficient for the specific trait.

At the level of the expression of a specific target gene, genetic engineering can bring about four types of change: reduced expression of a gene, complete loss of gene function, increased expression of a gene (including novel expression of a gene that is already in the plant in a tissue type in which it is not typically expressed), and introduction and expression of a new gene that is not found naturally in the target species or accession. Genome-editing approaches also make it possible to alter the coding sequence of an endogenous gene so that it encodes a protein with altered function (for example, an enzyme with altered catalytic properties or sub-

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[1] As noted in Chapter 7, the TILLING (conventional breeding) approach has a higher probability of unintended effects that result from changes to nontarget genes.

strate specificity); this altered gene could be a novel allele of a gene in the target species or a favorable allele of a gene present in another genotype of the target species. In all cases except the introduction of a novel gene into the target species, it is theoretically possible—although not necessarily practical—to introduce the trait without genetic-engineering approaches by using TILLING or genetic selection in most crop species. Genetic engineering may accelerate the process but would not be essential for reaching the desired end-point.

FINDING: New molecular tools are further blurring the distinction between genetic modifications made with conventional breeding and those made with genetic engineering.

FINDING: Treating genetic engineering and conventional breeding as competing approaches is a false dichotomy; more progress in crop improvement could be brought about by using both conventional breeding and genetic engineering than by using either alone.

FINDING: In some cases, genetic engineering is the only avenue for creating a particular trait. That should not undervalue the importance of conventional breeding in cases in which sufficient genetic variation is present in existing germplasm collections, especially when a trait is controlled by many genes.

PROJECTION OF HOW EMERGING GENETIC-ENGINEERING TECHNOLOGIES WILL AFFECT TRAIT DEVELOPMENT

The emerging genetic-engineering technologies discussed in Chapter 7 have the potential to change future crop production substantially with respect to quality, quantity, and applications because of the following three paradigm-changing capabilities in precision, complexity, and diversity.

Increased Precision of Genome Alteration and Gene Insertion

As discussed in Chapter 7, most GE crops commercially available in 2015 were engineered by using *Agrobacterium tumefaciens*-mediated or gene gun-mediated transformation, both of which result in insertion of the DNA into semirandom locations in the genome. Variation in expression of the transgene was observed routinely because of positional effects that depend on where in the genome the DNA was inserted; this required screening of large numbers of GE plants to identify the optimal transgenic individuals. The emerging technologies discussed in Chapter 7 enable insertions into specific locations in the genome that are selected to enable appropriate expression.

Like earlier genetic-engineering approaches, emerging genetic-engineering technologies can insert a gene from a very distantly related organism into the genome of the target species, but they also enable the modification of endogenous genes within a species. Such technologies as genome editing discussed in Chapter 7 permit a change or changes to one or more nucleotides in a genome and thereby focus trait alteration on a single targeted gene in a precise and predictable manner with few if any off-target changes.

Increased Complexity of Genomic Changes

Emerging genetic-engineering technologies have the potential to increase the complexity of engineered changes substantially because multiple genes can be introduced or "stacked" into a single target locus in which genes (transgenes, native genes, and cisgenes) are inserted as a "cassette" into the target locus. New paradigms—such as multiple genes for one trait, multiple genes for multiple traits, or, in some cases, one gene for multiple traits—are expected to be seen in future GE crops.

The ability to insert multiple genes expands the possibilities for the alteration of plants' natural metabolic pathways (metabolic engineering; Box 8-1). Metabolic engineering ranges from simple (modification of a single gene that changes flux in an existing pathway[2]) to complex (multiple genes manipulated to introduce a new pathway). If multiple genes have been used and are from different organisms or have been modified or synthesized de novo outside the organism of origin, the approach may be referred to as synthetic biology.

Increased Diversity of Engineered Crops and Traits

Perhaps the most dramatic change due to emerging genetic-engineering technologies is the diversity of the crops and traits that will be engineered. Although commercialized GE crops until 2015 were predominantly high-production commodity crops (maize, soybean, and cotton), the committee expects an increase in crop species that are genetically engineered and an expansion in the application of crop genetic engineering for food, feed, and human health.

> **FINDING: The emerging genetic-engineering technologies outlined in Chapter 7 will lead to increased precision, complexity, and diversity in GE crop development. Although genome editing is a new technique and its regulatory status was unclear at the time the committee was**

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[2] Flux is the flow of intermediate metabolites toward the final products.

BOX 8-1
Metabolic Engineering

Plant metabolic engineering is not new, although few plants modified using this approach had been approved for commercialization when the committee was writing its report. One example that cleared the U.S. regulatory system in 2014 was reduced-lignin alfalfa, produced by the companies Forage Genetics International and Monsanto. Reduced-lignin alfalfa is the result of metabolic engineering to reduce flux into the plant's endogenous lignin pathway by downregulation of a single gene that encodes an enzyme involved in the pathway; the outcome is engineered alfalfa with improved forage digestibility. Another example is high-oleic acid soybean, produced by DuPont and deregulated in the United States in 2010. It was the first of a series of genetically engineered plants whose fatty-acid composition was modified through metabolic engineering. The seed oil contains over 75-percent oleic acid; thus, it can be heated to higher temperatures, removing the need for chemical hydrogenation. The altered fatty-acid composition is achieved by downregulation through RNA silencing of two endogenous genes that encode fatty-acid desaturases (FADs). High-oleic acid soybean has also been generated in a non-GE product by combining mutant alleles of the FAD-2 and FAD-3 genes (Pham et al., 2012).

Future applications of metabolic engineering for plant improvement will probably take advantage of advances in synthetic biology to introduce ever more complex pathways. For example, oilseed crops have already been engineered to produce health-promoting polyunsaturated fatty acids through introduction of multiple genes from different species; the resulting plant oils have a composition closer to that of fish oil (Wu et al., 2005; Truska et al., 2009; Ruiz-López et al., 2012). In the future, plants could become production platforms for various industrial chemicals or pharmaceuticals, or the engineered metabolic changes might impart multiple stress tolerances, such as tolerance of drought and heat. Success in metabolic engineering through the introduction into a plant of multiple genes requires that the relative expression of the genes be such that no bottlenecks in the pathway to the required end product are introduced. Furthermore, the genes must be maintained as a cosegregating unit. The latter may be facilitated by the use of new delivery systems such as artificial chromosomes or placement of DNA cassettes into preselected sites in the genome via genome-editing approaches.

writing this report, the committee expects that its potential use in crop improvement in the coming decades will be substantial.

FUTURE GENETICALLY ENGINEERED TRAITS

Throughout this report, the committee has emphasized the idea that GE crops that were commercially available in 2015 had few engineered traits. That is expected to change in the future. Figure 8-1 summarizes a selection

Input traits

Stacked herbicide tolerance

Biotic stress resistance

Microbial resistance
- Major resistance genes
- Phytoalexin engineering[a]
- Novel resistance mechanisms[a]
- Viral RNA interference or coat protein[a]

Insect resistance
- Stacked insecticidal genes[a]
- RNA interference[a]

Abiotic stress tolerance
- Drought tolerance
- Water-use efficiency
- Cold tolerance
- Heat tolerance
- Salt tolerance

Nutrient-uptake and nutrient-use efficiency

Nitrogen fixation (in cereals)[a]

Phosphorus-use efficiency

Carbon fixation
- Improved Rubisco[a]
- C4 photosynthesis in C3 grasses[a]
- CAM in C4 plants[a]

Post harvest improvements
- Microbial resistance
- Increased shelf-life[a]
- Reduced bruising[a]
- Silage stability[a]
- Standardized quality

Output traits

Enhanced nutritional content
- Micronutrients
- Amino acids
- Vitamins
- Fatty acid profiles
- Flavonoids and nutraceuticals

Food safety
- Reduced acrylamide formation[a]
- Reduced aflatoxin concentrations[a]

Forage quality
- Digestibility
- Nitrogen protection[a]

Biofuels and industrial byproducts
- Ease of processing
- Improved biodiesel properties
- Advanced biofuels[a,b]

FIGURE 8-1 Traits that may be delivered with emerging genetic-engineering technologies.

[a] Traits that most likely can be developed only with genetic-engineering technologies or for which genetic engineering appears to be the most efficient approach.

[b] Advanced biofuels are fuels that are compatible with current infrastructure for processing and delivery.

NOTE: Input traits affect production practices on the farm, whereas output traits introduce changes that are relevant after harvest when a crop enters the food or feed supply chain. However, those categories are not mutually exclusive. For example, input traits can benefit yield (an output) under some environmental conditions (such as pathogen and weed pressure) while benefiting consumers by reducing a crop's exposure to disease or pesticides. Many potential future genetically engineered traits are predicted to be output traits, engineered specifically to change the quality of a crop. Most output traits developed in the coming decades will probably not require the use of chemical agents and should not require substantial changes in agricultural practices other than the requirement for identity protection and control of gene flow.

of potential future GE traits, and specific examples are described below. The list in Figure 8-1 is far from exhaustive. It contains examples that span the spectrum of development: initial trait identification or conceptualization, empirical proof-of-trait expression and function in plants, initial field testing, and preparation for commercialization.

Tolerance of Biotic Stress

Stress caused in plants by other living organisms is termed biotic stress. Resistance to insects through the incorporation of *Bacillus thuringiensis* (*Bt*) proteins into crops is an example of a GE form of tolerance of biotic stress. Most GE crops commercially available when the committee was writing its report were engineered to have resistance to herbicides or to biotic stress in the forms of insects and, to a much smaller extent, viruses. Research was being conducted on other ways to combat those stressors and on ways to provide protection against sources of biotic stress that had not yet been addressed with genetic engineering.

Resistance to Fungi and Bacteria

Resistance to many fungi and bacteria is controlled in plants by major resistance genes (*R* genes) that confer qualitative resistance (that is, resistance to a particular strain of a pathogen). However, pathogens can readily mutate to overcome resistance conferred by a single major gene—an example of the "evolutionary arms race." There is a long history of pathogens evolving to overcome resistance (*R*) genes introduced into crop varieties by plant breeders (Sprague et al., 2006; Stall et al., 2009). Plant breeders have therefore kept ahead of pathogens by introducing new varieties with combinations of different *R* genes that are found in plants in gene banks (Gururani et al., 2012). One problem with that approach is the time that it takes to discover and introgress new sources of resistance into elite varieties with conventional-breeding approaches. A detailed understanding of a plant species' repertoire of *R* genes, coupled with the ability to stack different natural resistance traits into a single variety by using emerging genetic-engineering technologies, could make it more feasible to respond rapidly to evolving pathogen virulence in the field (Jones et al., 2014), given appropriate infrastructure.

A group at Wageningen University in the Netherlands developed potato varieties with resistance to various strains of the late blight fungus *Phytophthora infestans*, the pathogen that caused the Irish potato famine in the 19th century (Box 8-2). The approach involved introduction of a set of different *R* genes, using only DNA sequences from potato (*Solanum tuberosum*), so that the resulting plants would be classified as cisgenic (Haverkort et al., 2008, 2009; see section "Transgenics versus Cisgenics versus Intragenics"

BOX 8-2
Durable Qualitative *R* Gene-Mediated Resistance of Potato to *Phytophthora*

From 2006 through 2015, a research project, Durable Resistance Against *Phytophthora* (DuRPh), was carried out at Wageningen University and Research Centre. Its objective was to develop a proof of principle for durable resistance to late blight (*Phytophthora infestans*) by using cisgenesis. The project was publicly funded by the Netherlands government. It aimed to stimulate research on genetic engineering in Europe's social environment, which was not conducive to such innovations, and to stimulate public debate on innovative genetic-engineering approaches. The researchers cloned and transferred major late blight *R* genes of crossable wild potato species (cisgenes) by using marker-free *Agrobacterium tumefaciens*-mediated transformation (that is, only the cisgenes were transferred). The goal was to introduce novel combinations of multiple *R* genes into established varieties. Within the framework of the project, 13 *R* genes from wild potato species were mapped, and three of them were cloned. More genes were mapped and cloned in parallel projects. Four varieties (Première, Désirée, Aveka, and Atlantic) were supplied with one to three *R* genes. Once the functioning of the *R* genes or *R* gene combinations was confirmed, marker-free transformation was conducted and successive cisgenic events were selected. After selection in the laboratory, late blight resistance was assessed with a detached-leaf assay and later in field tests. The researchers showed that inserted *R* genes are capable of turning a susceptible variety into a resistant one.

Resistance-management studies were conducted to determine how to deploy the *R*-gene combinations spatially and temporally to maximize resistance longevity through monitoring in the field. The experiments demonstrated the efficacy of combining multiple genes in disease control while reducing fungicide use by more than 80 percent. Communication through the news media and field demonstrations was extensive and contributed markedly to public debate and policy-making. Future deployment of the DuRPh approach will depend largely on whether the cisgenic approach is exempted from the prohibitions on use of GE crops in Europe. The approach is covered by patents, with a view to licensing of the technology to all interested potato-breeding companies and preventing monopoly use.

in Chapter 7). Even though multiple *R* genes can now be engineered into a crop from wild potato, it is still critical to use a rigorous management strategy to ensure that resistance is not overcome through pathogen evolution. The approach taken by the Wageningen team uses cassettes of different groups of *R* genes that can be deployed depending on field and computer simulation studies of pathogen spread and evolution. To be effective, such a deployment strategy would require a correspondingly rapid and flexible regulatory-approval system and the infrastructure to replace quickly varieties that are in use.

Box 8-2 provides an example of public research for public good—the cisgenic potato. This example illustrates concern for sustainability by conducting resistance-management research up front; this has not always been the case in conventional breeding of pathogen resistance.

An alternative approach to the engineering of single or combined major qualitative *R* genes involves the engineering of novel defense mechanisms. Proof-of-concept studies aimed at the reintroduction of the American chestnut (*Castanea dentata*) into the United States constitute an interesting example of this strategy from both the scientific and public perspectives. The American chestnut, which at one time accounted for 25 percent of the trees in eastern forests of the United States, was almost destroyed by chestnut blight (*Cryphonectria parasitica*), a fungus introduced from Asia in the early 1900s (Paillet, 2002). Some 3–5 billion trees have been killed by the fungus, and the fungus survives—but is nonpathogenic—on oaks (*Quercus* spp.); thus, the pathogen is fixed in the ecosystem. The Chinese chestnut (*Castanea mollissima*) has quantitative resistance to blight, but this involves over 20 genes, making backcrossing in trees with such long generation times difficult (Bauman et al., 2014). Resistance to chestnut blight has been engineered by introduction of a single gene, which encodes the enzyme oxalate oxidase, from wheat (*Triticum* spp.) (Zhang et al., 2013). Oxalate is produced by the fungus; fungal strains producing the highest levels of oxalate tend to be the more virulent strains. The products of the oxidase are carbon dioxide and hydrogen peroxide, the latter acting as the antifungal agent. Hydrogen peroxide is regulated by the U.S. Environmental Protection Agency (EPA) as a plant-incorporated protectant. Non-native chestnut and American chestnut lines generated by mutation breeding are also being planted. According to the American Chestnut Research and Restoration Project, should the GE chestnut be submitted to and ultimately approved by EPA (and any other regulatory agencies if needed), the GE trees will be initially introduced in areas currently devoid of trees, in botanical gardens, and on private land (Powell, 2015). On the basis of an estimated rate of spread of 8–10 trees that generated 4,000 trees over a period of 125 years in Wisconsin, the originators of the project predict that 40–400 million new chestnut trees could be established within 100 years if there is strong public support for planting the trees. That would represent about 10 percent of the trees lost to the disease (Powell, 2015).

Crops that are important staples in the diets of many people in developing countries include vegetatively propagated crops—such as sweet potato (*Ipomoea batatas*), banana and plantain (*Musa* spp.), and yam (*Dioscorea* spp.)—that are particularly susceptible to microbial infections. Despite decades of research, sources of natural resistance to devastating diseases in banana, such as Panama disease (a wilt caused by *Fusarium oxysporum* f.sp. *cubense*) and black sigatoka (a leaf-spot disease caused by *Mycosphaerella* *fijiensis*) remain elusive. Genetic-engineering approaches have potential to increase the speed with which new germplasm can be developed. For example, resistance to banana *Xanthomonas* wilt, a bacterial disease of increasing importance in east and central Africa, was enhanced by inserting the *Hrap* gene from sweet pepper (*Capsicum annuum*) (Tripathi et al., 2010). Of course, use of those genetic-engineering approaches will depend in part on public acceptance of the newly developed germplasm, in terms of both the technology and the actual varieties into which it is incorporated.

Another approach to improving resistance to pathogens is enhancing phytoalexin production; phytoalexins are antimicrobial compounds synthesized by plants after infection or stress (see Chapter 5, "Endogenous Toxins in Plants"). They make up a broad array of chemical classes that contribute to quantitative disease resistance, the best studied being of flavonoid or terpenoid origin. It is likely that the ability to produce some of those defensive chemicals may have been lost during domestication of major crops (Palmgren et al., 2015). Although proof of concept of plant protection through engineering of inducible defense compounds was obtained more than 20 years ago for a single-step pathway (Hain et al., 1993), the complexity of many phytoalexin pathways and the danger of evolved resistance to single antimicrobial compounds appear to have limited interest in the approach (Jeandet et al., 2013). Studies have begun to decipher the transcriptional control of induced small molecule defense pathways in plants (Mao et al., 2011a; Yamamura et al., 2015; Yogendra et al., 2015), allowing for coordinated expression and tissue-specific targeting of defense metabolites, even in the absence of knowledge of their complete biosynthetic pathways. Engineering transcriptional control mechanisms also facilitates the introduction of multiple antimicrobial defense molecules to reduce the chances of the pathogen evolving to overcome the introduced resistance. Regulatory scrutiny should ensure that the newly introduced or ectopically expressed metabolites do not adversely affect plant quality and food safety.

> **FINDING: A better understanding of both the nature and regulation of inducible defense pathways coupled with emerging genetic-engineering technologies could enable manipulation of complex metabolic pathways for enhancing plant resistance to disease.**

Resistance to Viruses

The mechanism of virus resistance in papaya (*Carica papaya*)—transgenic expression of viral coat protein—was discussed in Chapter 3. Cassava (*Manihot esculenta*), a major subsistence crop in sub-Saharan Africa, is susceptible to two serious virus diseases, cassava brown streak disease (CBSD) and cassava mosaic disease (CMD). CBSD first became a problem in Mozambique and is spreading to central and western Africa. Two research groups were working to develop virus-resistant cassava at the time the committee was writing its report. With a mix of federal, foundation, and corporate funding (from the Monsanto Fund, the U.S. Agency for International Development, the Bill and Melinda Gates Foundation, and the Howard G. Buffett Foundation), scientists at the Donald Danforth Plant Science Center, in collaboration with scientists in Uganda, Kenya, and Nigeria, were developing a high-throughput genetic transformation platform for farmer-preferred cassava varieties (Taylor et al., 2012) and were addressing cassava virus resistance through an RNA interference (RNAi) strategy. A similar approach was being taken by scientists at ETH Zurich (Nyaboga et al., 2013), introducing CBSD resistance into a Nigerian variety of cassava that is naturally resistant to CMD (Vanderschuren et al., 2012). Field trials suggest that those approaches are promising (Ogwok et al., 2012).

> **FINDING: Genetic engineering can be used to develop crop resistance to plant pathogens with potential to reduce losses for farmers in both developed and developing countries.**

Resistance to Insects

The use of single-protein and multiple-protein toxins from *Bt* in cotton (*Gossypium hirsutum*) and maize is widespread, but other insecticidal proteins have not become widely available in most commercialized crops. There has been considerable discussion about the use of RNAi, and the first RNAi maize variety was deregulated by the U.S. Department of Agriculture (USDA) in 2015 (USDA–APHIS, 2015). The RNAi strategy derives from usurping a natural cellular defense mechanism that cuts RNA from infectious organisms that invade cells (Fjose et al., 2001). The effectiveness of RNAi constructs such as double-stranded RNA (dsRNA)—introduced through ingestion of plant tissues—was first shown for the western corn rootworm (*Diabrotica virgifera virgifera*) (Baum et al., 2007) and cotton bollworm (*Helicoverpa armigera*) (Mao et al., 2007). The strategy was designed to silence genes critical for growth and development of specific insect pests without silencing genes in other organisms. The gene encoding DvSnf7, a protein essential for intercellular movement of membrane vesicles in the insect midgut, has been the most studied insect target (Koči et al., 2014), and DvSnf7 RNAi has been coexpressed with the Cry3Bb1 protein; the DvSnf7 RNAi and the Cry3Bb1 protein act independently against Colorado potato beetle (*Leptinotarsa decemlineata*) (Levine et al., 2015).

Developments in RNAi technology to protect crops against insect pests have also used novel approaches that depend on the chemical ecology of the host–herbivore interaction. In a project aimed at controlling cotton bollworm (Mao et al., 2007), dsRNA was targeted specifically against the insect cytochrome P450 enzyme CYP6AE14. Cytochrome P450s are ubiquitous enzymes that in animals and insects are involved primarily in the detoxification of foreign compounds. CYP6AE14 is involved in the detoxification of the cotton sesquiterpene gossypol, a potent antifeedant, and is induced by that compound. Lack of gossypol detoxification as a result of RNAi-targeted silencing of CYP6AE14 expression led to drastic reduction of bollworm larval growth on cotton plants that were engineered to express the CYP6AE14 dsRNA (Mao et al., 2011b).

A more complex example, which also illustrates the potential for genetic engineering to improve the understanding of complex ecological systems, concerns the expression in the tobacco species *Nicotiana attenuata* of dsRNA targeting the messenger RNA produced from the insect CYP6B46 gene; this gene encodes an enzyme that helps to direct a portion of the nicotine ingested by the insect *Manduca sexta* from the midgut to the hemolymph (analogous to the blood of vertebrates). Plants expressing the CYP6B46 dsRNA and nicotine-free GE plants were grown in their native habitat. Larvae of *M. sexta* feeding on either nicotine-free plants or plants expressing the dsRNA were attacked more frequently by nocturnal wolf spiders [*Camptocosa parallela* (*Lycosidae*)] than larvae feeding on *N. attenuata* that had not been engineered because the larvae feeding on nicotine-free plants exhaled no nicotine and those feeding on dsRNA plants exhaled less nicotine through their spiracles (Kumar et al., 2014). As might be expected, not all attempts to modify insect behavior via genetic engineering are successful; wheat engineered to express a gene from peppermint (*Mentha* × *piperita*) for production of the volatile insect pheromone E-beta-farnesene (which attracts predators of aphids) was protected from aphid damage in the laboratory but not in the field (Sample, 2015).

A technical limitation of expression of dsRNAs that are long enough to be gene-specific is the presence in plants of machinery to cut the long dsRNAs into short interfering RNAs. As described in Chapter 7, that limitation has been overcome by inserting the gene for the dsRNA into the plant's chloroplast genome rather than the nuclear genome.[3] With that alternative approach, the dsRNA accumulates in the chloroplast and is not exposed to the RNA-cutting enzymes in the cytoplasm. The strategy has proved effective for control of Colorado potato beetle by targeting the caterpillar's essential actin gene (Whyard, 2015; Zhang et al., 2015). Another report described the expression of dsRNA against the gossypol-detoxifying CYP6AE14 and other targets in tobacco chloroplasts (Jin et al., 2015) and concluded that the strategy was effective for insect control.

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[3] The chloroplast genome is part of the plastid genome.

The committee heard from invited speakers (for example, Hansen, 2014) and received and read comments submitted from members of the public voicing concerns about the potential for off-target effects on human gene expression through consumption of dsRNA molecules targeted against insects. A number of studies (Dickinson et al., 2013; Snow et al., 2013; Witwer et al., 2013) have contradicted the results of a previous study (Zhang et al., 2012) that dsRNAs originating in plants can accumulate in human tissues following ingestion, and, in 2014, an EPA scientific advisory panel likewise concluded that there were minimal risks from use of dsRNAs because of the degradation of such molecules in the human gut and the ability to design sequences that lack off-target effects.[4] As an additional precaution, the committee believed that targeting the dsRNA to a subcellular compartment in a nonedible portion of the plant could prevent exposure. For example, in the case of potato, the dsRNA could be expressed in the functional chloroplasts in the leaves but not in the amyloplasts in tubers. This additional targeting precaution would, of course, only be useful if the edible portion of the plant was not subject to attack by the insect that is targeted by the dsRNA.

The effectiveness of RNAi in controlling insects appears to be both species-specific and tissue-specific. For example, lepidopteran insects are generally poor targets for RNAi, and genes expressed in epidermal tissues are difficult to silence with RNAi approaches (Terenius et al., 2011).

Given that lepidoptera are naturally resistant to the effects of exogenous RNAi, it seems feasible that other insects could evolve resistance to RNAi. Whether other species of insects could downregulate or even lose their natural cellular RNAi machinery and thereby become resistant to this approach is not obvious. Acquired RNAi degradation pathways seem to be one potential mechanism for evolved resistance. Increased RNAi degradation could be a dominant or partially dominant trait based on the general finding that gain-of-function traits have this mode of inheritance (Gould, 1995), and the best resistance-management strategy could be to provide large refuges (see Chapter 4 section “Resistance Evolution and Resistance Management in *Bt* Crops”). The major concern is that one of these mechanisms could provide resistance against dsRNAs irrespective of sequence, so it would not be possible to overcome resistance by switching to new RNAi targets.

The committee heard concerns from members of the public at the workshop about the environmental effects of different pest-management practices and received and read submitted comments about off-target effects of RNAi on beneficial or endangered species. The concerns, which mirror

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[4] The meeting materials for the EPA scientific advisory panel on RNAi technology as a pesticide, including the meeting minutes, are available at http://www.epa.gov/sap/meeting-materials-january-28-2014-scientific-advisory-panel. Accessed March 9, 2016.

concerns addressed in environmental impact studies conducted for any GE crop, were:

- Effects on other (non-pest) herbivores consuming the same crop.
- Effects on predators or parasites that consume the herbivore.
- Gene flow to other plant species (less of an issue for chloroplast transformation).

When the committee was conducting its review, there was insufficient evidence to support or refute any of those concerns beyond the conclusion by USDA's Animal and Plant Health Inspection Service (APHIS) that a Monsanto transgenic event incorporating RNAi into maize to control corn rootworm did not pose an environmental risk (USDA–APHIS, 2015).

> **FINDING: Several genetic-engineering approaches involving use of RNAi or exploitation of chemical ecological phenomena are becoming available for the control of insect pests. More research is required to address the sustainability of, and off-target effects arising from, RNAi approaches and to learn how to adapt agroecological manipulation for crop protection.**

Tolerance of Abiotic Stress

Abiotic stresses to crops include cold, heat, drought, and soils with high concentrations of salts or other chemicals that inhibit plant growth. Although an understanding of the biochemistry of stress is far from complete, commercialization of some GE stress-resistant plant varieties has begun.

Tolerance of Drought

Plants cannot grow under severe drought, and strategies to enhance drought tolerance generally focus on better survival during drought so that if moisture returns plants can resume growth and yield loss will not be too great. Monsanto offers DroughtGard™ maize, a GE maize that expresses a gene encoding cold-shock protein B (cspB) from *Bacillus subtilis* (Castiglioni et al., 2008). Under some drought conditions, cspB expression seems to result in higher yield than non-GE controls, but more on-farm tests are needed.[5] Drought tolerance could be increasingly important in the face of climate change (Box 8-3).

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[5] Genuity DroughtGard Hybrids. Available at http://www.monsanto.com/products/pages/droughtgard-hybrids.aspx. Accessed November 20, 2015.

BOX 8-3
Resilience to Climate Change in Agriculture

Traits that respond to abiotic stress will be increasingly important in the face of anticipated climate-change effects. Two traits that stand out as especially important are thermal tolerance and drought tolerance (Howden et al., 2007). Enhancements of productivity in such crops as maize in Africa are expected by some to be for naught unless thermal tolerance and drought tolerance are enhanced (Folberth et al., 2014). Greenhouse and field trials of new varieties with GE traits under current climate conditions may have minimal relevance for climate in 2030 or 2040 (Bennett et al., 2014). As a result, there is a need to consider trait performance not just from the perspective of maximization of efficiency or yield but from the perspective of robustness, that is, minimizing the risk of total failure in an uncertain and extreme climate (Bennett et al., 2014). Climate stress also places a premium on improvements in such crops as cassava, which generally does not utilize irrigation or high inputs and can thrive in predicted climate scenarios (Jarvis et al., 2012). Finally, changes in climate will probably be accompanied by changes in pathogen and insect-pest populations in specific geographic locations, which will present a further challenge to resilience of future crops, GE or otherwise.

Some effects of climate change on crop production will be favorable; for example, increased carbon-dioxide concentrations will improve photosynthetic efficiency (Fischer et al., 2014). Increased carbon dioxide may also have unexpected effects; for example, cotton plants express the *Bt* toxin less strongly when grown in high carbon-dioxide concentrations (Coviella et al., 2002; Wu et al., 2007).

Although some regions will become drier, others will become wetter; climate change will be accompanied by increasing unpredictability of seasons and more frequent extreme weather events (IPCC, 2014). Climate change will affect both the yields and the quality of produce in a number of ways. Increased temperatures will speed crop development and thus limit potential yields. In colder climates, increased temperatures may extend the growing season, particularly of crops with indeterminate growth such as cotton (Bange et al., 2010).

The major focus of both conventional-breeding and genetic-engineering approaches is to select for traits that allow crops to withstand or avoid abiotic stresses and that can be combined with adapted management. For example, strategies to avoid heat stress include adjusting sowing dates or the phenology of crops, or both, to avoid periods of extreme temperature. Adjusting sowing times and providing supplemental irrigation may complement selection for or engineering of specific traits that endow enhanced drought tolerance.

Drought tolerance in plants involves multiple responses, so engineering of a single response protein may be less effective than mechanisms that can alert a plant to drought and activate a suite of responses. That may be feasible, as exemplified by a strategy that targets a receptor that responds to the drought hormone abscisic acid (ABA). A variant of the ABA receptor PYRABACTIN RESISTANCE 1 was engineered to possess high sensitivity to the agrochemical mandipropamid; spraying this compound was shown to enhance drought tolerance in GE plants (Park et al., 2015). A structural model of the ABA receptor suggests that it may be possible to engineer the molecule for activation by other chemicals. One attraction of this approach is that most soil-water loss in agricultural crops is from transpiration; attenuating transpiration in anticipation of drought will help to preserve soil moisture. A drawback of the approach in medium-size commercial farms is that drought often occurs in midseason when plants are large, and spray coverage must usually be accomplished by airborne equipment.

Tolerance of Cold

Another example of engineered abiotic stress tolerance is the development of cold-tolerant eucalyptus (*Eucalyptus* spp.) trees by the company ArborGen for cultivation in the United States. Cold tolerance was enhanced by GE expression of the C-Repeat Binding Factor 2 (CBF2) gene from *Arabidopsis thaliana* (Nehra and Pearson, 2011). CBF2 is a regulator of other genes that are involved in cold tolerance. Increasing CBF2 expression in some commercial eucalyptus hybrids results in greater cold tolerance, which permitted cultivation in regions of the southeastern United States where frost can occur. The potential for reducing growth by overexpression of CBF genes was mitigated by placing the CBF gene under the control of a cold-inducible promoter to limit its expression to conditions under which it is desirable. The GE eucalyptus lines also contain a gene-expression cassette that prevents pollen development and thereby restricts gene flow, although ArborGen claimed, in its petition to USDA for deregulation, that the existing biological limitations of eucalyptus species grown in the southeastern United States would themselves serve as an effective barrier to gene flow (Nehra and Pearson, 2011). ArborGen submitted the petition in 2011; when the committee conducted its review in 2015, the petition for deregulation was still pending.

As discussed in Chapter 7, most current examples of GE traits are based on one gene. As the fundamental understanding of the biochemical basis of why a specific stress inhibits plant growth or why some organisms are more resistant to a specific stress than others increases, so does the potential to use genetic engineering to enhance abiotic stress tolerance more effectively. It is increasingly likely that future enhancements of stress tolerance will require the introduction of several genes, possibly associated with metabolic engineering (see Box 8-1).

> **FINDING: Several approaches to engineering abiotic stress tolerance in plants are available, but, owing to the complexity of plant stress responses, more complex, temporally adjustable approaches than are**

now used will probably be necessary, particularly in the face of unpredictable climate change.

Increasing Plant Yield and Efficiency of Production

Increasing plant yield in absolute terms, as opposed to overcoming the yield gap (as defined in Chapter 4), has always been a major goal of conventional plant breeding. In commodity crops—such as maize, soybean, and wheat—additional yield gain as a result of breeding is generally incremental, at an average of about 1–2 percent per year, although there have been historical exceptions when the introduction of such innovations as hybrid maize or semi-dwarf wheat and rice increased yields considerably (see Chapter 2 section "The Development of Genetic Engineering in Agriculture" and Chapter 4 section "Potential versus Actual Yield"). Examples of future genetic-engineering approaches to improve plant yield or increase the efficiency of production include improving nutrient-use efficiency, introducing nitrogen fixation, and re-engineering primary metabolism, particularly increasing the efficiency of photosynthesis.

Nutrient-Use Efficiency

Nutrient-use efficiency (NUE) refers to plant yield relative to the nutrients (for example, fertilizer components) used to achieve that yield. Many factors influence NUE, including the extent of the root system, how effectively root cells can take up nutrients, and how readily nutrients are transported from root to shoot. Modifying any of these factors in a manner that increases productivity is likely to require several genes that are specific to the factors. For example, using genetic engineering to alter the extent and pattern of a root system is likely to require changing the expression patterns of many genes that control development, whereas increasing the efficiency with which roots take up nutrients could involve altering membrane transporter-protein concentrations or types.

Concerns surrounding the depletion of the world's mineable phosphate supply make phosphorus-use efficiency an especially important area for plant science research. Plant roots possess both high-affinity and low-affinity phosphate transporters (Poirier and Jung, 2015). Phosphorus sensing and uptake are under complex regulation (Scheible and Rojas-Triana, 2015) and are linked to root development, so simply overexpressing high-affinity phosphate transporters is not in itself a solution. An emerging understanding of the regulators of phosphate sensing, uptake, and response is leading to strategies that use genetic engineering to improve phosphorus-use efficiency in plants (Gamuyao et al., 2012; Wang et al., 2013). It has also been suggested that phosphorus-use efficiency could be improved by altering the distribution of phosphorus in the plant (Veneklaas et al., 2012); this would involve the manipulation of multiple genes. Finally, engineering plants to secrete phosphatase enzymes that release phosphate from organic constituents of soil has also been shown to improve plant phosphate-use efficiency (Wang et al., 2009).

Nitrogen Fixation

Nitrogen is a key nutrient that often limits plant growth. “Fixing” nitrogen refers to converting nitrogen gas in the atmosphere into a form that can be incorporated into biological molecules. Plants are not able to fix nitrogen directly, but some bacteria are. However, legumes, such as soybean and common bean (*Phaseolus vulgaris*), have evolved the ability to associate in an intimate symbiotic relationship with some species of nitrogen-fixing bacteria and thus are able to produce a crop without added nitrogen fertilizer or organic amendments. In spite of the greater nitrogen-use efficiency of legumes (such as soybean) as compared to cereals (such as maize), in agricultural production it is often economically advantageous to grow legumes with added nitrogen fertilizer to ensure reliable yields because the additional cost of the fertilizer is not prohibitive.

Nitrogen-fertilizer production uses a substantial amount of natural gas—a fossil fuel—whereas biological nitrogen fixation does not, so engineering biological nitrogen fixation has an environmental benefit. There are two possible routes to enabling plants to fix sufficient nitrogen to support high yields. One is to introduce genes encoding all the proteins involved in nitrogen fixation. That is a complex undertaking because the nitrogen-fixation system is a bacterial metabolic pathway; many aspects of plant metabolism would need to be modified to support biological nitrogen fixation in plants, and this in turn would require introduction or alteration of many genes. Furthermore, a cellular compartment with low oxygen concentration would have to be engineered or adapted to support the nitrogen-fixing activity. Another route is to enhance the plant–bacterial nitrogen-fixation interaction in the legume species in which it naturally occurs so that more nitrogen fixation is supported or to engineer genetic networks needed for nitrogen-fixing symbiosis into plants that do not normally have this interaction.

Those approaches were discussed at a meeting of the Gates Foundation in 2011 (Beatty and Good, 2011), which led to the foundation’s support of basic research toward the goal of engineering nitrogen fixation in cereals. The Gates Foundation funded two approaches that address different aspects of engineering cereals to fix nitrogen. One focuses on engineering the genes that could allow cereals to form nodule structures similar to those found in legumes that house nitrogen-fixing bacteria (Rogers and Oldroyd, 2014). The other focuses on synthetic engineering of the nitrogen-fixing enzyme nitrogenase with the aim of inserting the necessary genes into plastids or mitochondria (Curatti and Rubio, 2014). The necessary approaches to engineering nitrogen fixation in cereals will involve synthetic biology to re-engineer pathways affecting both cell biology and plant metabolism (Rogers and Oldroyd, 2014). Even with the technologies on the horizon, engineering nitrogen fixation or a mechanism for a novel symbiosis is a daunting challenge, so it is not possible at present to judge whether this will be successful.

The commitment to face that challenge is complemented by the Gates Foundation's projects aimed at tailoring and adapting existing legume technologies for smallholder farmers in Africa through its N2Africa program.[6]

Increasing Efficiency of Photosynthesis

Another example of altering metabolism to increase productivity is improving the efficiency of photosynthesis, which in turn could increase the rate of plant growth and probably yield (Bräutigam et al., 2014; Weber, 2014). One limitation to photosynthetic efficiency is that the enzyme (commonly referred to as RuBisCo) that initiates the process of converting carbon dioxide to sugar (commonly referred to as carbon fixation) can also react with oxygen in a side reaction that wastes energy. The magnitude of the side reaction with oxygen is a function of the relative amounts of carbon dioxide and oxygen that RuBisCo encounters. Some plants have evolved a way to mitigate the side reaction: RuBisCo and carbon fixation are restricted to cells in which carbon dioxide is accumulated through shuttling by four-carbon compounds such as malate (this type of metabolism is referred to as C4). Maize has C4 metabolism. Introducing C4 metabolism into crops, such as rice, that do not have it could increase yields. Re-engineering rice carbon-fixation metabolism would, however, require the manipulation of many genes, including ones that control leaf development and leaf differentiation (to create specialized cells for carbon fixation) and ones that encode the enzymes of C4 metabolism. The International Rice Research Institute has embarked on a long-term project to develop C4 rice.[7]

Another approach to mitigating the side reaction of RuBisCo with oxygen is to change the enzyme in such a way that it can no longer interact with oxygen but continues to carry out the carbon-fixation reaction. Although in principle that is a simple "single-gene" solution of the problem of the side reaction, in practice it has proved quite difficult to accomplish. Perhaps the difficulty is not surprising inasmuch as throughout the course of evolution

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[6] N2Africa: Putting nitrogen fixation to work for smallholder farmers in Africa. Available at http://www.n2africa.org/. Accessed December 12, 2015.

[7] The C4 Rice Project. Available at http://c4rice.irri.org. Accessed December 12, 2015.

there has been an extensive opportunity for the side reaction to be eliminated by the random mutations that continually arise in populations. One would expect if such a mutation did arise that it would provide a selective advantage, but this has not happened. Rather, many organisms have independently evolved a variety of carbon dioxide-concentrating mechanisms that increase photosynthetic efficiency, one of which was discussed above. Nevertheless, if scientists discover a way to make a "better" RuBisCo, it would be a substantial advance toward increasing plant productivity. RuBisCo from the cyanobacterium *Synechococcus elongatus* fixes carbon dioxide more rapidly than plant RuBisCo and has been expressed in tobacco chloroplasts in place of the native tobacco enzyme as a first step in engineering improved carbon-fixation efficiency (Lin et al., 2014); the plants were photosynthetically competent, but further engineering to raise the local carbon-dioxide concentration in the vicinity of the enzyme and suppress the oxygenation reaction is still needed.

> **FINDING: Applications of genetic engineering that target basic plant processes, such as photosynthesis and nitrogen fixation, have the potential to result in greater yield gains or increased efficiency but will probably require complex genetic changes and therefore involve long-term projects.**

Increased Forage Quality

Lignocellulosic biomass (in the form of plant stems and leaves) is the major feedstock for forage-based milk and meat production. Many of the cattle in the United States and elsewhere are fed alfalfa, a high-protein forage. Genetic engineering can introduce traits into alfalfa and other sources of feed that will improve digestibility and animal nutrition and reduce health risks for ruminant livestock associated with methane production.

Digestibility

Lignification of cell walls in forage adversely affect digestibility by ruminant animals because it restricts access of the digestive system's microorganisms and enzymes to cellulose and hemicellulose polymers that together make up the bulk components of both primary and secondary cell walls in plants (Ding et al., 2012). Those polymers are made of hexose (six-carbon) and pentose (five-carbon) sugar units, the major carbon sources for animal nutrition after degradation of the polymers in the rumen. The inherent properties of the lignocellulosic materials, collectively called recalcitrance, have proven difficult to alter with conventional-breeding methods (Dixon et al., 2014). Although the phenomenon of cell-wall recalcitrance is complex and probably involves multiple chemical entities and mechanisms, the presence of a lignin in secondary cell walls is a major contributor (Chen and Dixon, 2007; Ding et al., 2012).

Lignin is a complex aromatic polymer derived primarily from hydroxycinnamyl alcohols (monolignols) that are linked into the lignin polymer by a seemingly random free-radical polymerization process in the plant cell wall (Boudet et al., 1995). Lignin is deposited in secondary cell walls of plants after they have stopped expanding and imparts structural integrity to the cell wall, strength to stems, and hydrophobicity to vascular elements for water transport.

The quality of alfalfa hay is assessed on the basis of protein content and fiber digestibility; however, as an alfalfa-hay crop increases in biomass, the quality of the forage decreases, owing in large part to lignin deposition. Reduced-lignin (RL) alfalfa, developed by Forage Genetics International in partnership with Monsanto, was deregulated in the United States in late 2014; it was engineered to contain reduced amounts of lignin in secondary cell walls through partial silencing of the gene encoding an enzyme involved in the synthesis of the monolignol building blocks of lignin. RL forages should allow the farmer to balance optimal biomass with quality, and this should translate into an increased window during which the crop can be harvested.[8] Increasing the digestibility of alfalfa should decrease the amount of alfalfa that needs to be grown per kilogram of meat or milk produced, thereby decreasing the amount of land needed per kilogram of meat or milk. It should also reduce the amount of manure generated per kilogram of forage.

The reduction in lignin content (by around 10 percent) places RL alfalfa at the limits of, or even outside, the normal variation in lignin content for this species; this is because alfalfa has been highly improved, and there is not a wide range of natural variation in biomass digestibility among varieties. Alfalfa is indigenous to southwestern Asia, having probably originated in Iran, so gene flow from RL alfalfa in the United States and most of the world would result in transfer of the low-lignin trait only to other commercial alfalfa crops or perhaps to feral populations around commercial plantings. The major risk associated with gene flow from RL alfalfa is probably an economic one: the contamination of non-GE alfalfa, including organic alfalfa. That risk is therefore similar to the one arising from herbicide-resistant (HR) alfalfa and has to be managed to take into account the pollination method of the crop.

The second potential risk associated with RL alfalfa—one that will be relevant for many products of plant metabolic engineering—comes from

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[8] At the time this report was written, Forage Genetics International was preparing to market RL alfalfa under the brand name of HarvXtra™. RL varieties of alfalfa with and without glyphosate resistance were in development.

the partial disruption of a natural metabolic pathway in the plant, with a potential for flow of intermediates into other pathways and different branches of the targeted pathway (in this case lignin). The lignin in RL alfalfa has an increased proportion of sinapyl alcohol monolignol–derived residues. When that was first observed, it was unexpected and viewed as an unintended effect until it was discovered that alfalfa has a route by which the downregulated enzyme could be bypassed in the synthesis of sinapyl lignin (Zhou et al., 2010). That highlights the importance of basic science to provide understanding to help in risk assessment.

Alfalfa contains a number of natural products with known bioactivity, some of which are biosynthetically related to lignin. As discussed in Chapter 5 (see section "Endogenous Toxins in Plants"), isoflavones are antimicrobial compounds with perceived benefits for human health but might also have adverse effects because of their estrogenic properties. Targeted analysis of isoflavones in RL alfalfa did not detect significant changes compared with those in non-GE commercial lines. The triterpene saponins are molecules with antiherbivore properties; alfalfa contains a wide array of these compounds, which have different profiles in foliage and roots. Triterpene saponins at high concentrations can exhibit hemolytic activity in monogastric animals, such as horses. Triterpenes were unaffected in RL alfalfa relative to their concentrations and compositions in non-GE commercial lines. Other members of the genus *Medicago*, to which alfalfa belongs, exhibit wide natural variation in triterpene saponin content. It therefore seems logical that saponin concentrations should also be evaluated during the breeding of non-GE alfalfa and other *Medicago* species, such as the annual *Medicago truncatula*, which is used as a forage legume in Australia. Finally, alfalfa sprouts contain canavanine, a neurotoxic nonprotein amino acid. Canavanine concentrations were somewhat lower in RL alfalfa than in non-GE commercial lines.

Because RL alfalfa results in more biomass than alfalfa with normal lignin levels before quality reduction forces harvest, a new factor is introduced into the management of the crop. The quality of single-trait HR alfalfa decreases with increasing maturity in the same way as in nonreduced lignin alfalfa, and HR alfalfa is therefore harvested earlier than RL alfalfa may be harvested. That raises the question of whether RL alfalfa will be more likely to be left to flower in the field and thereby to increase the risk of pollen flow to non-GE alfalfa. To address that possibility, Monsanto has applied restrictions on the growing of RL alfalfa to "include managing hay to prevent seed production, harvesting at or before 10-percent bloom in areas where seed is produced, and prohibitions on use in wildlife feed plots. Growers who raise alfalfa for seed would be required to follow Forage Genetics International Best Practices" (USDA–APHIS, 2011).

Nitrogen Protection and Mitigation of Methane Production

One of the major disadvantages of high-protein forages is the potential for causing pasture bloat arising from excess methane production in the rumen. Methane is an important greenhouse gas. The presence of natural products called condensed tannins (CTs) can protect ruminant animals from potentially lethal bloat. CTs are polymers of flavonoid units (products of plant secondary metabolism) that bind to proteins and therefore reduce the rate of fermentation in the rumen and reduce methane production. Their protein-binding activity also allows more intact protein to leave the rumen, and this results in improved nitrogen nutrition. Alfalfa foliage lacks CTs, and their introduction has been an important but not yet realized goal of alfalfa breeding. In addition to alfalfa, introducing or increasing CTs into other forages—such as clover (*Trifolium* spp.), ryegrass (*Lolium* spp.), and grazed wheat—and seed crops used in animal feed, such as cotton and soybean, is a goal. Higher CT concentrations can also prevent long-term spoilage of silage.

Although not all the biochemical reactions leading to CTs in plants are fully understood, several studies have attempted to increase CTs in plant foliage through genetic engineering. It is a complex metabolic-engineering problem because of the need to express multiple genes in a tissue in which they are not normally expressed. One approach to engineering of changes in expression of multiple genes is to use genes that encode transcription factors (TFs). TFs are proteins that bind to the regulatory regions of genes and modify the magnitude of expression of the genes; they may be positive or negative regulators. Often, a single TF will regulate multiple genes in a biochemical pathway and thus obviate separate genetic manipulation of the individual steps in the pathway. TFs that control the genes for the CT pathway have been discovered, and it has been shown that one such TF, from a species of clover that produces high concentrations of CTs, can turn on accumulation of CTs when expressed in alfalfa leaves (Hancock et al., 2012). It therefore seems likely that the CT traits will be engineered into forage species through modification or synthesis of new TFs that activate expression of genes responsible for synthesis of CTs. That raises several scientific and regulatory issues.

TFs themselves are usually expressed at very low levels in plant cells, and a substantial body of evidence suggests that they may have different effects, depending on the magnitude of their expression, with a potential for off-target effects when expressed at unnaturally high levels (Broun, 2004). Humans consume CTs and their precursors in large quantities in foods and beverages, such as chocolate and red wine, in which they are perceived to provide health benefits (see discussion on high-anthocyanin tomatoes in “Flavonoid Antioxidants” section below). In contrast, high concentrations of CTs can be astringent and therefore act as antifeedants. Assuming that genetic engineering can lead to the moderate concentrations of CTs required to improve animal health and performance, the major regulatory issue is unlikely to be the CT product itself and more likely ensuring that there are no problematic off-target effects resulting from TF expression.

> **FINDING: Increased understanding of basic plant sciences will enable better prediction of off-target changes that could be caused by genetic engineering.**

> **FINDING: GE approaches to forage-quality improvement have potential to yield environmental benefits associated with reductions in greenhouse gases and manure.**

Improved Biofuel Feedstocks

The last decade has seen intensive research on the development of “second-generation” biofuels derived from lignocellulosic materials, mainly trees, such as poplar (*Populus* spp.), and grasses, such as switchgrass (*Panicum virgatum*) and *Miscanthus* (Himmel et al., 2007; Poovaiah et al., 2014). Use of both GE and non-GE approaches will be necessary to deliver biofuel crops that are sustainable agronomically and economically. In particular, reducing the recalcitrance of plant biomass to enzymatic deconstruction to develop crops that can be directly deconstructed and fermented to liquid biofuels (consolidated bioprocessing), and incorporating coproducts to the residual biomass to add value, have been identified as major goals (Mielenz, 2006; Ragauskas et al., 2006, 2014).

The efficient release of fermentable sugars from plant cell walls is the first critical step in the conversion of lignocellulosic biomass to liquid biofuels, such as ethanol or iso-butanol, or to other industrial chemicals produced by fermentation. The recalcitrance of lignocellulose to deconstruction to its component sugars is an important factor that limits the economics of the cellulosic-ethanol industry (Himmel et al., 2007). Since 2010, many proof-of-concept studies have indicated the feasibility of reducing the recalcitrance of biomass, and thereby increasing ethanol yields, through the engineering of cell-wall polymers in both bioenergy crops and model species such as *Arabidopsis thaliana*. Most of the studies have targeted lignin (Li et al., 2014; Liu et al., 2014) on the basis of the same mechanistic principles that underlie the improvement of forage digestibility discussed above. However, it is becoming clear that recalcitrance is a complex trait that also involves cellulose, hemicellulose, and pectic cell-wall polymers and cell-wall cross-linking by small molecules. It is therefore likely that future improved bioenergy crops will have genetic changes in multiple pathways that are introduced through the techniques of genome or RNA editing, transformation with multigene cassettes, or combining of transgenes through conventional-breeding approaches (Kalluri et al., 2014). Furthermore, to avoid potentially deleterious effects of strong lignin reduction in critical tissues, such as water-conducting vessels, the genetic changes will be targeted to specific tissue types by using either tissue-specific gene promoters to drive downregulation of target genes or more complex strategies, such as pathway rewiring by modifying regulatory sequences (Yang et al., 2013). Reduced recalcitrance may also be combined with additional engineered traits, such as increased biomass density to reduce the volume of the crop that needs transportation (Wang et al., 2010). Some of those approaches will require engineering of TFs, which will raise issues similar to those discussed above in connection with metabolic engineering of CTs.

Potential future lignocellulosic bioenergy crops include perennial grasses (such as switchgrass and *Miscanthus*), rapid-rotation coppiced trees (such as willow, *Salix* spp.), other trees (such as poplar and eucalyptus), and drought-tolerant succulents (such as *Agave* spp.). Some of these species are only poorly domesticated, so there might be considerable natural variation in multiple traits, including cell-wall composition and recalcitrance, and this is now being experimentally confirmed. An analysis of over 1,000 natural variants of poplar (*Populus trichocarpa*) growing in the Pacific Northwest of the United States revealed an extreme range of lignin content (Studer et al., 2011), with low lignin equating to reduced recalcitrance. Natural variation in cell-wall composition is also seen in switchgrass (Vogel et al., 2011). Those observations suggest that reduced recalcitrance can be introduced into some bioenergy crops through conventional breeding. In trees with long generation times, genetic engineering could reduce the time to a commercial product compared with conventional breeding.

Risk assessment of reduced-recalcitrance trees and grasses would probably be similar to that of RL alfalfa discussed above, with the extra issues of preventing and monitoring gene flow to native populations for indigenous species, such as switchgrass and poplar, and the long time scale for assessment of true environmental effects for many trees. Gene flow from outcrossing perennial grasses could be prevented by engineering pollen ablation or sterility, traits that may themselves present additional regulatory issues. An inquiry to USDA–APHIS regarding GE switchgrass from Ceres Inc. sought exemption from regulation, claiming that the cassettes used for transformation were introduced by particle bombardment and therefore contained no plant-pest–derived DNA; the exemption was granted (Camacho et al., 2014). The justification was that the plant event did not meet the requirements of being or containing components of a plant pest (see Chapter 9 section "Regulatory Implications of Emerging Genetic-Engineering Technologies"), rather than evaluation of potential risks associated with its reduced-lignin trait's being conferred on native populations of switchgrass.

Another approach to development of bioenergy crops is to produce the fuel directly in the crop. The best-known example is biodiesel, and a number of oilseed crops have been used as sources of biodiesel. Examples are soybean, canola (*Brassica napus*), *Camelina sativa* (a relative of canola), and *Jatropha curcas*. The latter has been grown over wide areas in Asia and sub-Saharan Africa, although the economic viability of the crop, on the basis of seed yields, is a matter of debate (Jingura and Kamusoko, 2014). Genetic improvement of biodiesel properties will involve both oil yield and oil quality. There is a considerable body of work on genetic engineering of plant oil quality, much of it associated with improving nutritional quality by reducing concentrations of saturated and trans-fatty acids (see below). Much of the work on GE improvement of oil quality and yield for biodiesel has been in green algae, yeast, and bacteria, rather than in plants (Hegde et al., 2015). However, *Camelina* has emerged as a potential new oilseed crop, on which genetic knowledge from the related model plant *Arabidopsis thaliana* can be translated for production of oils for food, industrial, or biofuel applications (Vollman and Eynck, 2015); in the latter case, high oleic oils are preferred.

Some plant species naturally produce hydrocarbons at varied concentrations, either constitutively or after insect or pathogen attack. A good example is the production of terpenes in trees, such as pine (*Pinus* spp.) and eucalyptus. Knowledge of the genes involved in terpene synthesis in plants has facilitated synthetic-biology approaches to the engineering of microorganisms to produce sesquiterpenes, such as farnesene, that can be used directly as fuels (Wang et al., 2011), and genetic engineering of increased concentrations of such compounds directly in plants is possible (Beale et al., 2006). A potential problem with that latter approach is the volatile nature of the terpenes, which either are released in small amounts as signal molecules in plant–insect interactions (Beale et al., 2006) or are stored naturally in larger amounts in specialized glands in plants that naturally accumulate high concentrations of the compounds (King et al., 2004). In the absence of such glands in such species as *Camelina sativa*, it may be necessary to convert the terpenes to less volatile forms, through conjugation to sugars or other molecules, to facilitate accumulation.

> **FINDING: Recent advances in understanding and overcoming biomass recalcitrance make it more likely that "second-generation" lignocellulosic biofuels will be developed commercially through either conventional breeding or genetic engineering.**

Introduced or Enhanced Nutritional Traits

Humans require at least 50 nutrients, including vitamins, essential amino acids, essential fatty acids, minerals, and trace elements. Particularly in developing countries, those requirements are not being fully met by the prevailing agriculture; staple crops are poor sources of some critical nutrients (Welch and Graham, 2005; also see Chapter 5 section "Improved Micronutrient Content").

Plant breeding has generally focused selection on crop yield and, in the case of fruits and vegetables, on taste and processing properties. During the roughly 10,000 years that humans have been farming, the few common crops that are mostly used for human consumption have lost many of their phytonutrients (Robinson, 2013). A detailed examination of nutrient compositional changes of 43 garden crops from 1950 to 1999 suggested a loss of six nutrients (protein, calcium, phosphorus, iron, riboflavin, and ascorbic acid) (Davis et al., 2004)—with the caveat that one needs to factor in differences in sampling methods, varieties chosen for analysis, analytical methods, and growing environment. An example of a comparison of cultivated versus wild red raspberries collected from one of the germplasm centers in Turkey showed that some wild accessions had higher antioxidant activity and phytonutrient contents (Çekiç and Özgen, 2010). When the genes for high phytonutrients are no longer found in germplasm collections, genetic engineering could be the only practical approach for restoring phytonutrient concentrations.

Engineering of Vitamins and Polyunsaturated Fatty Acids

Among the best-publicized examples of GE improvements in nutritional content are Golden Rice engineered to contain high concentrations of provitamin A beta-carotene and oilseed engineered to contain high concentrations of polyunsaturated fatty acids (PUFAs). Conventional breeding and advances in MAS can lead to improvements in nutritional composition of plants that already contain the nutrients in question and whose germplasm pool varies widely in the trait (Graham et al., 1999; Welch et al., 2000; Welch and Graham, 2005; White and Broadley, 2005; Goldman, 2014). In the cases of provitamin A and PUFAs, genetic engineering has been used when the natural germplasm does not contain the genes necessary to deliver the trait. The pros and cons of Golden Rice have been discussed extensively, and the arguments will not be recapitulated here (see discussion in Chapter 5 section "Improved Micronutrient Content").

Metabolic engineering of health-promoting PUFAs, with profiles similar to those found in fish oils, has been more complex than the engineering of provitamin A, and in some cases requires the introduction of multiple genes from different species (Wu et al., 2005; Truska et al., 2009; Ruiz-López et al., 2012). Eicosapentaenoic acid and docosahexaenoic acid have been engineered to accumulate up to 20 percent of the seed oils of GE *Camelina sativa* with no effects on growth phenotype in the greenhouse (Petrie et al., 2012; Ruiz-Lopez et al., 2014) or the field (Usher et al., 2015). Oil from the GE plants was shown to be effective in replacing fish oils in salmon-feeding trials (Betancor et al., 2015).

Engineering of Mineral Micronutrient Concentrations

Major essential micronutrients for humans that can be deficient in staple diets include iron, zinc, copper, selenium, and iodine. Simple agricultural measures, including soil fertilization and amendments or crop rotations, may have little effectiveness in improving micronutrient concentrations in grains (Rengel et al., 1999); delivering micronutrients to vulnerable human populations through traditional methods, such as supplementation or food fortification, can likewise be ineffective because of complex political and socioeconomic factors (White and Broadley, 2005). Although new technologies have the potential to deliver needed micronutrients, they may be limited by the same political and socioeconomic factors that have made it difficult to deliver improved nutrition through non-GE food.

A large multinational research endeavor to genetically engineer increased iron and zinc concentrations in cassava was going on when the committee was writing its report (Sayre et al., 2011; Sayre, 2014). Those two micronutrients were identified previously as commonly deficient in most regions of the developing world, and such deficiencies could be addressed through genetic engineering (Zimmerman and Hurrell, 2002). Iron was increased in the cassava root by using the iron-specific assimilatory protein from *Chlamydomonas reinhardtii*, which enhanced iron uptake from the soil. Iron increased from about 10 to 40 ppm. The strategy used for zinc was to introduce additional plasma-membrane zinc transporters for higher accumulation of zinc in the tuber. Introduction of the *Arabidopsis* ZIP[9] zinc transporter gene caused increase in root zinc concentrations of 2 to 10 fold, but decreased zinc in the plant leaves adversely affected yield; thus, this approach needs refinement.

Three independent genetic-engineering approaches that target iron transport to and storage in the seed endosperm were combined to produce rice with 440 percent more iron without reducing yield (Masuda et al., 2012).

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[9] ZRT-IRT-like proteins (ZIPs) are a family of plant membrane transporters, originally assigned to zinc and iron transporters.

Although both GE micronutrient-enhanced cassava and rice are precommercial, there were efforts toward commercialization when this report was being written.

Reduced-Phytate Maize

Phytate is a phosphorus storage sink for essential plant metabolic activities, but its composition of inositol plus up to six phosphates creates a dense negatively charged molecule that binds cationic minerals, particularly iron and zinc, rendering them inaccessible to the body during digestion and absorption. Conventional-breeding and genetic-engineering approaches have been used to reduce phytate content to increase bioaccessibility of those essential minerals. Genome editing with zinc finger nucleases was successfully used to reduce phytate concentrations in maize (Shukla et al., 2009). Edited plants were fertile, and the low phytate content was observed to transfer to next-generation plants. However, the technology had yet to be commercialized as of 2015.

Increasing Availability of Essential Amino Acids

For humans and most mammals, lysine is the limiting essential amino acid in most cereal-based diets and is particularly deficient in maize grain. The latter is because the maize storage protein, zein, is very low in lysine. Efforts to improve protein quality began in the 1950s, when reports of a large protein deficit in populations in the developing world spurred government-led research to find improved protein-quality cereal genotypes. High-lysine maize was found as a naturally occurring mutant and was termed *opaque2* maize; lysine and tryptophan (the second limiting amino acid in maize) contents were about double those of normal maize (Mertz et al., 1964). Soft kernels and otherwise poor grain quality made for poor adoption, but conversion to a hard endosperm type by the International Maize and Wheat Improvement Center (CIMMYT) in Mexico increased its potential, and this variety is now used in some parts of Africa and other areas (Vasal, 2000). Genetic-engineering techniques have also been used to increase lysine content of soybean, rapeseed, and maize with a number of approaches (Galili and Amir, 2013). Expression of a bacterial feedback-insensitive dihydrodipicolinate synthase of lysine synthesis, which increases free lysine, was used to make a high-lysine maize (Lucas et al., 2007), but it was never released.

Flavonoid Antioxidants

Anthocyanins are the well-known red and purple pigments found throughout much of the plant kingdom as major natural products in fruits and flowers. They have antioxidant activity and have been linked to a number of potential health benefits (Yousuf et al., 2015). Anthocyanins consist of a flavonoid molecule (an anthocyanidin) conjugated with one or more sugar molecules and sometimes other chemical groups. The anthocyanidins are intermediates in the formation of the condensed tannins discussed above. Because plants naturally contain anthocyanins, their concentrations can be increased in fruits and vegetative tissues through conventional breeding if sufficient natural variation is present. However, attempts are being made to increase the concentrations of anthocyanins beyond the ranges found naturally, to introduce anthocyanins into fruits that generally lack them, and to engineer related flavonoids, such a flavonols, in fruit tissues through genetic-engineering technologies or by isolation of mutants (Dixon et al., 2012). Basic proof-of-concept studies in this field have been conducted on various vegetable and fruit species, including apple (*Malus* spp.), grape (*Vitis* spp.), tomato (*Solanum lycopersicum*), and cauliflower (*Brassica oleracea*). The related condensed tannins have also been the subjects of similar studies in fruits and vegetables, with the purpose either of reducing their concentrations to decrease astringency in high-tannin fruits, such as persimmon (*Diospyros* spp.) (Akagi et al., 2009), or of increasing their concentrations to provide health benefits.

Although tomato plants can produce anthocyanin pigments in their vegetative tissues, the main pigments giving the red coloration to tomato peel and flesh are carotenoids. The peel contains low concentrations of flavonoids in the form of chalcone glycosides (conjugated precursors of flavonols and anthocyanins) and flavonols, but the fruit is deficient in potentially beneficial anthocyanin antioxidants. Although some heritage tomato varieties have a purplish skin, it was probably not due to the presence of anthocyanins. Conventional-breeding approaches have generated tomatoes with anthocyanins in the skin but not in the flesh.[10] Anthocyanin-rich "purple tomatoes," with anthocyanin throughout the flesh, are being developed through genetic engineering. The strategy has involved the expression of two TFs that naturally control anthocyanin formation in the flowers of the snapdragon (*Antirrhinum majus*) (Butelli et al., 2008; Gonzali et al., 2009). In one small study, the high-anthocyanin tomatoes were reported to delay tumor development when fed to cancer-susceptible mice (Butelli et al., 2008), but effects on human health require more detailed studies (Tsuda,

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[10] The Purple Tomato FAQ. Available at http://horticulture.oregonstate.edu/purple_tomato_faq. Accessed November 20, 2015.

2012). Furthermore, the shelf-life of the tomatoes was doubled as a result of a slowing of the over-ripening process, and this led to a reduction in infection by the fungus *Botrytis cinerea*. When the committee was writing its report, high-anthocyanin tomatoes were in greenhouse trials in Canada. Similar approaches with expression of maize TFs (Bovy et al., 2002) or over-expression of the enzyme chalcone isomerase (Muir et al., 2001) have been used to engineer tomato fruits with high concentrations of flavonols, similar to ones in onions (*Allium cepa*), but not accompanied by accumulation of anthocyanins. High-flavonol GE tomatoes were as acceptable in consumer taste studies as non-GE varieties (Lim et al., 2014).

Because the enhancement of flavonoid concentrations in the GE tomatoes does not occur at the expense of carotenoids, which are also beneficial to health (Johnson, 2002), high-flavonoid/anthocyanin tomatoes may indeed provide substantial health benefits to consumers. Studies in animal models suggest that high concentrations of anthocyanins can be consumed without adverse health effects (Pojer et al., 2013). Potential risks include the possibility of off-target effects resulting from TF overexpression; transcriptome analysis has shown that multiple pathways, including defense responses, are activated because of the expression of the two TFs in high-anthocyanin tomatoes (Povero et al., 2011). Natural variation in anthocyanin concentrations in several fruits and vegetables has been shown to be controlled by differences in expression or naturally occurring mutations in similar TFs, so conventional breeding could also be used to increase anthocyanin concentrations, although probably not in tomato flesh.

Finally, high-anthocyanin grapes have been granted nonregulated status by USDA–APHIS, on the basis of their being cisgenic and generated with gene gun-mediated transformation (Camacho et al., 2014).

FINDING: Genetic engineering can enhance the ability to increase the nutritional quality and decrease antinutrients of crop plants.

Food-Safety Traits

Two examples of GE traits that led to improved food safety are low acrylamide in potato and an association of *Bt* in maize with lower fumonisin content (see Chapter 5). The low-acrylamide potato was developed by Simplot Plant Sciences through silencing of the asparagine synthetase-1 gene (Waltz, 2015). Acrylamide is one of the byproducts of the Maillard reaction between asparagine and reducing sugars that can occur in high-heat processing and is associated with cancer in rodents. The company has shown a 50–70 percent reduction in acrylamide in the GE potatoes compared with non-GE potatoes (see Chapter 5 section "Genetically Engineered Crops with Lower Levels of Toxins" for health implications).

Postharvest Traits

Postharvest traits that could be improved with genetic engineering span disease resistance of harvested fruits and grains, resistance to bruising, extended shelf-life, and standardization of taste and other qualities. For forage crops, silage stability could be improved. New GE traits for disease resistance are discussed above and are applicable to fruits and grains. Stability of proteins during ensiling of forages may be improved through engineering of tannins, as discussed above. Damage during bruising can be caused by both oxidative browning and cell lysis as a result of loss of integrity of internal cell membranes. As described in Chapter 3, oxidative browning can be reduced in fruits and other plant parts by downregulation of the polyphenol oxidase gene, as exemplified by the GE nonbrowning apple and potato; this could improve storage quality.

FUTURE GENETICALLY ENGINEERED CROPS, SUSTAINABILITY, AND FEEDING THE WORLD

Agriculture is the largest land use on the planet, accounting for 40 percent of Earth's land area (Foley et al., 2005). Worldwide demand for food is expected to double by 2050 (Tilman et al., 2011), and there is a risk that more natural habitat will be converted to agriculture to meet this demand with consequently huge losses in biodiversity.

Sustainable Intensification

It is well documented that most new agricultural land in recent decades has been created by deforestation in highly diverse tropics, and this makes the link between agriculture and conservation clear (Gibbs et al., 2010). From 1998 to 2008, cropland expanded by 48,000 km^2/year in tropical countries (Phalan et al., 2013). For that reason, many conservationists have suggested that sustainable intensification, by which they mean increasing yields per hectare without adverse environmental effects, is important for biodiversity conservation (Garnett et al., 2013).

The key question for the purposes of this report is the extent to which current and future genetic-engineering technologies can promote sustainable intensification (Godfray et al., 2010). Among the traits that have the potential to enhance sustainable intensification are improved forage quality for livestock (less land required and reduced methane production), disease and insect resistance, nutritional fortification, drought tolerance, salinity tolerance, and increased nitrogen-use efficiency (Godfray et al., 2010). Some of those traits have already been improved through conventional breeding and genetic engineering, but as discussed in the sections above, emerging genetic-engineering technologies coupled to increased understanding of plant biochemistry are expected to enable breeders to address traits that cannot be further improved by existing technologies.

Because 30–40 percent of the world's food is never consumed or is lost to waste, modifications that enhance storage properties could also reduce agriculture's demand for converting natural lands (Godfray et al., 2010). Whereas GE crops may play a role in decreasing yield gaps in ways that support sustainable intensification, it is important to point out that closing yield gaps and boosting agricultural production in many parts of the world will require improvement in agroecologically sustainable farming, irrigation, and fertilizer use (Mueller et al., 2012). In that respect, the International Assessment of Agricultural Knowledge, Science, and Technology for Development emphasized the need to expand agroecological knowledge and practices to meet growing food demands (IAASTD, 2009; Vanloqueren and Baret, 2009). It is also important that investment in GE crops is not made at the expense of developing agroecological approaches to intensification (Vanloqueren and Baret, 2009).

> **FINDING: It is important to develop policy approaches that enable research on GE crops to assist in achieving sustainable intensification without diminishing resources available for the exploitation of proven existing technologies.**

Sustainability and the Food System

A 2015 National Research Council report, *A Framework for Assessing Effects of the Food System*, asserts that determining how any given change will affect the food system is complex but that most studies seeking to measure how changes in agriculture affect the food system tend to have a narrow focus. The report contained a number of principles that should guide research on the food system. One is that it is important to consider four domains to predict effects on the food system: health, environment, social, and economic (NRC, 2015). That principle is meant to address the tendency to frame concerns about new technologies primarily in terms of health and environmental effects. It has been the goal of the present committee to incorporate these four dimensions into the analysis of experiences and prospects of GE crops.

Questions about the role that future GE crops can play in promoting a more sustainable agriculture and food system need to be addressed within those four domains (Hubbell and Welsh, 1998; Ervin et al., 2011; Macnaghten and Carro-Ripalda, 2015). There is a general recognition that sustainability should be understood to have health, economic, and social dimensions (especially in relation to equity of distribution of risks and benefits) in addition to environmental dimensions (Ervin et al., 2011). For example, Pfeffer (1992) traced the rise of the sustainability movement itself to farmer resistance throughout the 20th century to "appropriationism," the replacing of an on-farm activity with an industrial input. Furthermore, after reflecting on perspectives among regulatory agencies, scientists, and members of the public on how GE crops might contribute to sustainable agriculture and food in Mexico, Brazil, and India, Macnaghten and Carro-Ripalda (2015) advocated for moving beyond technical arguments about health and environmental risks and what they called stale debates grounded in polarizing positions. They argued instead that the key question is what institutional frameworks are necessary to generate social benefits from technology and that the social and ethical dimensions of this question need to be central. Marden et al. (2016) also directed attention to institutional concerns in what they referred to as the intellectual-property–regulatory complex. Their edited volume highlighted how intellectual property and regulatory frameworks can hinder or promote particular kinds of agricultural innovation and pointed to the need for creative approaches to managing the intellectual-property–regulatory complex.

There are promising new developments in GE crop research in the context of sustainability as defined above, but in most cases the analysis of the fit of new crops and traits with sustainability is assessed only at the environmental level. Even in considering that one domain, the focus of studies can be narrow. A good example is a high-profile GE crop study (Su et al., 2015) that was aimed at reducing the 7–17 percent of total methane in the atmosphere that is produced by farming rice (Bridgham et al., 2013; Kirschke et al., 2013). In the research, Su et al. (2015) engineered a GE rice line that captures more of its starch production in stems and seeds so that there is less starch in the roots. The goal behind the research was to develop a rice plant that provided a less suitable root environment for methane-producing bacteria and thereby mitigated greenhouse gas emissions. The work of Su et al. (2015) was a small experimental study to determine proof of concept, and clearly additional studies will be needed before deployment. In a commentary on the article, Bodelier (2015) noted areas that such future studies should address. For example, more nitrogen inputs may be needed to compensate for the loss of specific bacteria around the roots that deliver plant nutrients, and this could lead to nitrate leaching into the soil and production of more nitrous oxide, a potent greenhouse gas (and other geochemical cycles could be altered as well). Also, a change in root-associated bacterial populations might favor rice pathogens. Of course, there might also be unexpected benefits that become apparent as additional studies are conducted. Further research should be done to determine how the development and diffusion of a crop with the traits in question would be evaluated with respect to contributing to economic concentration, affecting farm structure and access by small and medium-size farmers, increasing access to food for all, and other social and economic effects that have been addressed in connection with current GE crops in Chapter 6. The committee cautions that it is important that conclusions based on such analyses not be drawn prematurely without knowledge of the properties of the finally developed crop that is to be deployed.

The committee outlines above (see section "Nutrient-Use Efficiency" one approach to increasing phosphorus-use efficiency by engineering plants to secrete phosphatase enzymes that cause the release of phosphate in the farm soil (Wang et al., 2009). While it may prove effective in the short run, a broader view must consider that the reserves of phosphate in the soil will become depleted with time.

From a similar perspective, it is worth examining GE drought tolerance carefully. This trait is considered difficult to engineer, even with emerging genetic-engineering technologies, but is generally considered desirable. That may be true at a general level, but the committee could find no detailed analyses of the long-term effects of different mechanisms of drought tolerance in different environments. If maize or another crop is engineered to be more drought-tolerant, it could become economically profitable in the short term to plant it in drier uncultivated land and thus decrease biodiversity. In some areas, a crop is grown only every other year so that the moisture in the soil can be replenished. With a drought-tolerant variety that had deeper roots, at least initially, the crop could be grown every year until water availability decreased further. There is clearly a need to conduct detailed systems analyses to anticipate long-term effects on environmental sustainability.

Lobell et al. (2014) found that as drought tolerance of conventionally bred maize varieties increased, farmers in the Midwest United States tended to use higher seeding rates to achieve higher yield. However, the higher plant density extracted more water from the soil, which left maize plantings more sensitive to drought. There is a tradeoff between using conventionally bred or GE maize with drought tolerance to maximize yield and using it to guard against losses from drought.

With respect to sustaining health, it is reasonably clear that increasing micronutrients or decreasing fumonisin and aflatoxin concentrations by using genetic-engineering technologies, though challenging to achieve, can improve health in some of the poorest populations of humans (see Chapter 5 section "Foods with Additional Nutrients or Other Healthful Qualities"). The effects of increasing anthocyanins and phenolics on well-nourished populations are less clear because it is unknown whether there are optimal concentrations and whether they could be exceeded. If emerging genetic-engineering technologies could protect plants against most insect pests and pathogens and thereby dramatically reduce the use of synthetic pesticides, there is little doubt that there would be favorable health effects as long as the GE foods themselves did not have any adverse health effects. Each trait in each crop, environment, and farming system must be considered carefully.

As discussed in connection with current GE crops in Chapter 6, social and economic effects are hard to evaluate, especially on the basis of data on initial adoption. Future GE crops that include multiple traits could be developed in ways that exclude access by resource-poor farmers or that provide traits that are not of much use to such farmers. Social and economic sustainability are more likely to be determined on the basis of the goals of the trait and crop developers than of the technology itself.

> **FINDING: Although emerging genetic-engineering technologies have the potential to assist in achieving a sustainable food system, broad and rigorous analyses will be necessary to determine the long-term health, environmental, social, and economic outcomes of adding specific crops and traits to an agroecosystem.**

The Role of New Genetically Engineered Crops and Traits in Feeding the World

One of the critical questions about new traits and crops that may be enabled by emerging genetic-engineering technologies is the extent to which these products will contribute to feeding the world in the future. As noted above, Tilman et al. (2011) concluded that by 2050 the global crop demand will be about twice what it was in 2005. It has been predicted that genetic engineering could have a major role in achieving the doubling of crop production (Leibman et al., 2014).

On the basis of the committee's review of the literature, various degrees of uncertainty are associated with the potential of new GE traits and crops to contribute to increased food production. As judged by accomplishments through commercialized GE traits and crops in decreasing damage from insect pests (and to a lesser extent pathogens) reviewed in Chapter 4 and the progress with emerging technologies described in this chapter, there is a strong expectation that new GE traits will be able to reduce losses from insects and pathogens while decreasing the use of synthetic pesticides as long as care is taken to decrease problems related to pest evolution of resistance to new crop traits. Many new GE traits will not increase yield potential but will decrease yield variation, especially by avoiding crop failures due to outbreaks of insect pests and pathogens. The traits could be especially valuable to resource-poor farmers if they are developed in a way that makes their adoption possible by these farmers and assures the public of their safety and if they are not lost due to the evolution of resistance in insect pests and pathogens.

It has been estimated that damage from insect pests and pathogens decreases crop yield by 45 percent, but this is disputed (Yudelman et al., 1998). It will be important to conduct in-depth studies to gain better estimates of how much protection from insects and pathogens could increase global food production. In an in-depth analysis, Savary et al. (2000) examined losses to rice throughout Asia because of insects, pathogens, and weeds (Savary et al., 2000). They found that total losses were on average 37.2 percent of the yield without biotic stresses. However, over 20 percent of the yield loss was from weeds; the main target for *Bt* rice, the stem borer (*Scirpophaga incertulas*), only caused an average loss in yield of 2.3 percent. The three major pathogens caused 1–10 percent of the yield loss. Damage estimates differed among rice production systems. These results emphasize the need to carefully assess how any specific intervention with GE traits will contribute to the goal of doubling food production.

As discussed in this chapter, increasing overall yield by engineering more efficient photosynthesis and nutrient use or by increasing drought tolerance is feasible, but there is uncertainty about the degree of success that will come in developing such traits in the future. Given the early stages of the research, even detailed reviews and assessments will not be able to predict how much increase in overall crop production will come from these efforts.

As explained in Chapter 6, feeding the world involves much more than simply increasing crop production. The choices of who invests in new crops and traits, what specific crops and traits are invested in, and other factors such as availability of institutional support and access to inputs will affect how much emerging genetic-engineering technologies will contribute to feeding the world. The policy-makers who will in part determine those choices have the heavy responsibility of gathering information on ways to optimize investment in emerging genetic-engineering technologies that will address the four domains of sustainability discussed above.

FINDING: Given the uncertainty about how much emerging genetic-engineering technologies will increase crop production, viewing such technologies as major contributors to feeding the world must be accompanied by careful caveats.

RECOMMENDATION: Balanced public investment in 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.

CONCLUSIONS

Genetic engineering and conventional breeding are complementary approaches, and more progress in crop improvement will be made by using both conventional breeding and genetic engineering than by using either alone. A greater understanding of the genetic basis of complex traits, such as drought tolerance and nitrogen-use efficiency, will require basic research investment in both approaches, although some complex traits are unlikely to be introduced without genetic engineering. The research on complex traits is at too early a stage to predict which traits will and will not be successfully developed. The specific traits that will be available to farmers and the specific crops and varieties in which the traits will be available will depend on the extent of investment in crop improvement by the private and public sectors. Beyond technical hurdles, future ecological, social, and economic issues and the regulatory landscape will affect decisions in research investments by the public and private sectors and the diffusion of new discoveries. It is critical that investment in solutions involving genetic engineering not diminish investment in other technologies already shown to efficiently increase sustainable crop production and nutrition.

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9

Regulation of Current and Future Genetically Engineered Crops

Given the controversies and broad spectrum of interests surrounding genetic engineering in agriculture, it is not surprising that different countries have developed and adopted diverse regulatory approaches to genetically engineered (GE) plants, crops, and food. The elements of scientific risk assessment are broadly similar among regulatory systems, but policy decisions—which inherently reflect different political and cultural perspectives on risks and benefits—vary considerably. Different cultural traditions, environmental and other societal conditions, and risk tolerances influence decision-makers, and they face political pressures from diverse groups—environmental and food-safety groups, organic-crop producers, large-scale farmers, animal producers, consumers, multinational agricultural companies, and other entities involved in the complex global food production and distribution chain.

As noted in Chapter 3, some regulatory systems reflect policies that are more permissive toward GE crops and foods[1] and others reflect policies that are more precautionary. A number of countries have adopted a "process-based" approach to regulation in which foods and crops that have been modified through a specified set of genetic-engineering techniques are

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[1] The term *GE foods* is used here as a shorthand way to refer to various food and feed products produced from GE crops, but few foods were directly "genetically engineered" when the committee was writing its report. Instead, most GE foods contain ingredients derived from GE plants (predominantly maize and soybean). The term is also used to refer to feed, the grains and other products from GE crops fed to animals. However, the term does not include the use of food-processing agents, such as chymosin produced from GE bacteria because these are not "crops" and are therefore beyond the scope of this report.

subject to premarket regulatory safety review for food safety and environmental protection, whereas new foods and crops that have similar traits and were developed through other breeding technologies are not. In addition, as noted in Chapter 6, some regulatory systems for GE crops and foods go beyond food safety and environmental protection to address economic and social issues, such as protecting non-GE agricultural production systems, providing information to consumers through product labels, and taking account of other social and economic concerns.

This chapter reviews illustrative examples of regulatory systems and compares regulation of GE crops with regulation of crops developed through conventional plant breeding. It also analyzes the implications of the emerging genetic-engineering technologies discussed in Chapter 7 for risk, risk assessment, and the scope of GE crop regulatory systems in 2015. Finally, the chapter reviews several critical issues regarding the regulation of current and future GE crops and offers several general and specific recommendations regarding the U.S. regulatory system. The regulatory issues reviewed include the role of product-approval systems in addressing social and economic issues, such as labeling and coexistence; the relationship between expert decision-making and democratic processes, including transparency and public participation; post-approval regulatory authority; and the appropriate scope of premarket regulatory review for plants that have novel traits, including GE crops.

REGULATORY SYSTEMS FOR GENETICALLY ENGINEERED CROPS

In this section, the committee first reviews international agreements that have relevance to the regulation of GE crops and then provides examples of the regulatory systems in three countries and the European Union (EU) to demonstrate different approaches that national or regional governments may take in the oversight of GE crop commercialization.

International Frameworks

To a considerable extent, international trade and other agreements constrain the domestic-product regulation policies of countries that are parties to the agreements. The World Trade Organization (WTO) agreements and the Cartagena Protocol on Biosafety are particularly relevant to the regulation of GE foods and crops.

Safety Assessment of Genetically Engineered Foods

National food-safety regulatory systems of countries that are party to the WTO must be consistent with principles established in the WTO

Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement).[2] The SPS Agreement governs measures to protect human, animal, or plant life or health, including food safety. While acknowledging the right of governments to enact such measures, the SPS Agreement also recognizes that such measures can operate as a de facto trade barrier and therefore sets out requirements to minimize trade barriers. Among other things, the SPS Agreement requires that measures be based on scientific principles and not maintained without scientific evidence except measures under Article 5 on which scientific information is insufficient. In such a case, a country may proceed to regulate but must also seek to resolve the scientific uncertainty. To promote harmonization of measures, the SPS Agreement recognizes international standards and guidelines developed by the Codex Alimentarius Commission and several other international organizations. Countries may adopt measures that are stricter than international standards if they are based on appropriate risk assessment. Countries may not adopt measures that are more trade-restrictive than needed to achieve the appropriate level of protection.

To increase the likelihood that countries regulate food safety on the basis of scientific principles, in 2003 the Codex Alimentarius Commission issued guidelines for assessing the safety of foods derived from plants that have recombinant DNA (CAC, 2003a) and principles for risk analysis of foods derived by modern biotechnology[3] (CAC, 2003b). The principles refer to risk analysis as including three components: risk assessment, risk management, and risk communication (CAC, 2003b). Risk assessment—an evidence-based process for characterizing the risks posed by a product—is a critical component of the SPS framework (Box 9-1). Countries that follow the Codex risk-assessment process in their domestic GE food-safety regulatory systems are in compliance with the SPS Agreement. As noted in Chapter 5 (see section “Substantial Equivalence of Genetically Engineered and Non–Genetically Engineered Crops”), the EU and many national GE food-safety regulatory systems have incorporated the Codex guidelines.

In general, the Codex guidelines and principles direct developers of GE foods to provide information that enables regulators to assess a variety of food-safety risks:

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[2] This discussion focuses on WTO agreements. Many regional and bilateral trade agreements contain similar provisions.

[3] The Codex definition of *modern biotechnology* comes from the Cartagena Biosafety Protocol under the Convention on Biological Diversity. It is defined as the application of in vitro nucleic acid techniques, including recombinant DNA and direct injection of nucleic acid into cells or organelles or the fusion of cells beyond the taxonomic family that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection (CAC, 2003b).

BOX 9-1
Risk Assessment and Risk Management

Risk assessment is an evidence-based process by which potential adverse effects of hazards are characterized. Risk assessment was originally developed as a method for assessing the overall health risk to individuals or populations exposed to some hazardous substance or situation (NRC, 1983), but it has been adapted and refined for additional purposes, including the assessment of environmental risks (for example, EPA, 1998; EFSA, 2010).

Risk assessment typically includes four steps (NRC, 1983):

1) Hazard identification: The identification of possible causes of harm, including an assessment of the strength of the evidence of causation. An example of hazard identification in terms of toxicology is whether a particular chemical could cause cancer or other adverse human health effects. In environmental risk, an example is whether agricultural chemicals could harm the reproduction of beneficial insects.
2) Dose–response assessment: The determination of the relationship between exposure and the probability of the adverse effect.
3) Exposure assessment: The determination of the extent of human or environmental exposure, taking into account possible regulatory controls.
4) Risk characterization: The description of the nature and, to the extent possible, the probability and magnitude of the health or environmental harm, including attendant uncertainty.

Risk is a function both of hazard and of exposure; it is the probability of a harmful effect, given the magnitude and type of exposure to the hazard.

Risk management is the process of determining the restrictions or controls needed to reduce human health or environmental risks to "acceptable" levels. What is acceptable is inherently a value-laden concept and depends on particular applications, environmental and other societal conditions, and societal judgments about the appropriate balance of tradeoffs between benefits and risks and their distribution. In some cases, laws provide decision standards or a process for making decisions about what is considered acceptable.

- Description of the GE plant (the crop involved and the nature of the genetic modification event or events).
- Description of the host plant and its use as a food, including the host plant's cultivation and breeding development and any known toxicity or allergenicity issues.
- Description of donor organisms, including any toxicity or allergenicity issues associated with them.
- Description of the genetic modifications, including details of the method of transformation, the DNA used, the vectors used, and any intermediate hosts that might have been used in the process.

- Characterization of the genetic modifications, including the number and nature of DNA insertions and border regions, the expression of the inserted DNA sequences, and a determination as to whether the expression of any other genes in the host plant has been affected.
- Safety assessment, including
    - —Expressed substances (non–nucleic-acid substances): An examination of the toxicity of any expressed products resulting from the genetic event and an evaluation to ensure that toxic components from a donor organism have not been inadvertently transferred. In the case of proteins, it is expected that amino acid sequences will be characterized and the potential for allergenicity determined.
    - —Compositional analysis of key components: An examination of key components of the host plant in comparison with the transformed plant. Plants are generally field-trialed under conditions that closely resemble commercial production, and natural variations in key components are considered in any evaluation.
    - —Evaluation of metabolites: An evaluation of metabolites that might be produced in the GE plant but not in the original host. The metabolites, if present, need to be assessed for their potential effect on human health.
    - —Food processing: Studies that explore the effects of food-processing treatments on components or metabolites of GE foods. The focus is to determine whether an altered protein or metabolite might become toxic after processing in contrast with components of the non-GE counterpart.
    - —Nutritional analysis: Same as the compositional analysis except when the genetic insertion is intended to change a key nutritional component, in which case additional testing may be needed to determine the level of the nutrient in question and its effects on human health, taking into account normal consumption patterns and the stability of the trait in multiple production environments.

Environmental Risk Assessment of Genetically Engineered Crops

The WTO Agreement on Technical Barriers to Trade (TBT Agreement) governs a broader set of measures and standards than the SPS Agreement and is intended to address such standards as those designed to protect the environment, promote national security, prevent deceptive marketplace practices, and protect human health and safety (apart from food-safety issues) and animal or plant life or health. The TBT Agreement recognizes the right of governments to adopt such measures but encourages the use of relevant international standards and nondiscriminatory practices to reduce barriers to trade. Recognizing the broader scope of such measures and different risk preferences in every country, the TBT Agreement does not require such measures to be based on scientific principles but instead emphasizes the nondiscriminatory nature and trade effects of such measures. In other words, the TBT Agreement provides countries with broader latitude than does the SPS Agreement in determining what levels of protection are appropriate. However, if new scientific information shows that the circumstances that gave rise to a measure are no longer valid—so that a perceived risk is found not to exist—the measure would have to be reviewed.

There is no recognized international expert scientific body equivalent to the Codex Alimentarius Commission in environmental protection. Some early international work on the topic of environmental risk assessment of GE crops was carried out by the Organisation for Economic Co-operation and Development (OECD) (OECD, 1986, 1993). The Ad Hoc Technical Expert group of the Cartagena Protocol on Biosafety also develops risk-assessment roadmaps (UNEP, 2014). The approaches to environmental risk assessment of GE crops (or "living modified organisms," LMOs) adopted by various countries share many elements but differ in level of detail and in specific considerations (EFSA, 2010; Flint et al., 2012).

The 2000 Cartagena Protocol on Biosafety (Biosafety Protocol), developed under the 1992 Convention on Biological Diversity, addresses potential environmental concerns that might be posed by introducing LMOs—such as GE seeds or plants that could propagate—into countries through international trade.[4] (It does not apply to pharmaceuticals or goods produced from GE crops, such as cotton or soybean oil, but some provisions apply to GE foods, including GE feed and processing ingredients.) The Biosafety Protocol calls for "Advance Informed Agreements" (AIAs) between exporting and importing countries regarding an initial shipment of an LMO and requires labeling of later shipments of that LMO.[5] The purpose of an AIA is to enable an importing country to assess potential environmental risks posed by the LMO before its introduction (through trade) into the country. The Biosafety Protocol expressly adopts the "precautionary principle" that allows countries to deny the importation of a GE product if they consider that there is not enough scientific evidence that

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[4] The Cartagena Protocol on Biosafety defines a *living modified organism* as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology." The Biosafety Protocol uses the same definition of modern biotechnology as the Codex Alimentarius Commission (see footnote 3).

[5] Many major agricultural exporting nations—including the United States, Argentina, Australia, Canada, and Russia—have not ratified the Biosafety Protocol. Nevertheless, U.S. companies involved in international grain trading comply with the requirements of importing countries.

the product is safe (Box 9-2). The Biosafety Protocol has been the main impetus for food-importing developing countries to develop biosafety approval and regulatory systems under its guidelines. The Biosafety Protocol's Supplementary Protocol on Liability and Redress establishes a liability mechanism for preventing and redressing environmental harm, but it was not in force when the committee was writing its report. Progress had been made in implementing functional biosafety policies in developing countries, but "translating policy into practice has been slow and laborious," especially in African countries (Chambers et al., 2014). According to Chambers et al. (2014), commercial GE crops were cultivated in only four African countries,[6] and there were confined field trials in six more.[7] Other countries were in various stages of developing policy or enacting biosafety legislation when the committee was writing its report.

Socioeconomic Considerations

Both the SPS Agreement and the TBT Agreement represent efforts to reduce impediments to trade by limiting what member countries may do through regulations or practices to create de facto trade barriers. As discussed above, in the case of food safety, restrictions must be based on scientific evidence regarding risk assessment, but other kinds of regulation have more leeway to incorporate nonsafety or socioeconomic issues that represent the diverse values of different countries. The reasons for the differences among countries regarding governance of socioeconomic issues related to GE crops are multifaceted and, as mentioned earlier, include different cultural traditions, values, risk tolerances, and political pressures exerted by diverse groups. Despite those differences, the WTO gives greater weight to scientific evidence related to safety (as opposed to values or fairness) in settling trade disputes, so consideration of socioeconomic issues receives little support in resolving trade disputes between countries. For example, in 2003, the United States, Canada, and Argentina brought a trade-dispute case under the WTO, alleging that the EU had violated the SPS Agreement through its de facto moratorium on approvals of genetically engineered food and feed (WTO, 2006). In its decision, the WTO Dispute Resolution Panel noted that the products had each been reviewed and approved on the basis of a scientific risk assessment and that the EU had not challenged those previous decisions. In its decision, the panel declined to apply the precautionary principle as an established principle of international law and also declined to apply provisions of the Biosafety Protocol, noting that the Biosafety Protocol was not binding on all WTO members (Henckels, 2006).

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[6] Burkina Faso, Egypt (until 2012), South Africa, and Sudan.

[7] Ghana, Kenya, Malawi, Nigeria, Uganda, and Zimbabwe.

BOX 9-2
The Precautionary Principle

Generally speaking, precaution involves taking measures to avoid uncertain future risks. The "precautionary principle" is a policy approach related to the regulation of risks to health, safety, and the environment. The term is used in different ways and contexts by different people, sometimes to include ethical and socioeconomic factors and sometimes not to. Different versions of it have been incorporated into a number of international agreements, including the Cartagena Protocol on Biosafety (NRC, 2002; Hammit et al., 2013), article 5(7) of the WTO SPS Agreement, and other trade agreements. A version of the precautionary principle included as Principle 15 of the Rio Declaration on Environment and Development states that "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." Other formulations and interpretations have been proffered (see, for example, EC, 2000), but the most salient component of the precautionary principle is its use of social values in making decisions on the side of protecting health, safety, and the environment in situations characterized by scientific uncertainty (Stirling, 2008; Von Schomberg, 2012). One example of the precautionary principle is that the United States and other countries prohibit the importation of drugs that the would-be importer cannot demonstrate as safe. In practice, decisions under the precautionary principle favor "false-positive" regulatory errors (erroneous findings that a product is harmful) over "false-negative" answers (erroneous findings that a product is not harmful).

The precautionary principle has been the subject of extensive debate. Many commentators attack it as nonscientific, irrational, ambiguous, and expensive for innovation (see, for example, Bergkamp and Kogan, 2013; Marchant et al., 2013). Critics have noted that because there is always some scientific uncertainty, the precautionary principle provides no clear and predictable basis for decision and therefore must be applied in an arbitrary manner (Marchant and Mossman, 2004). Proponents of the precautionary principle respond that risk-assessment regulatory

One example of regulation regarding a socioeconomic issue that is not science-based is mandatory labeling of GE foods. As discussed in Chapter 6, a number of countries have adopted mandatory labeling of GE foods on the grounds that labels provide information that enables consumer autonomy and choice. That rationale avoids the need to provide scientific substantiation for the claim that GE foods need to be labeled because they are less safe than non-GE foods. When the committee was writing its report, mandatory labeling of GE foods had not been challenged in the WTO. In 2011, the Codex Alimentarius Commission, which had a standard for GE-food labeling under consideration for a number of years, abandoned the effort in the face of disagreement (CAC, 2011; Miller and Kershen, 2011).

approaches also inherently involve subjective judgments in the face of scientific uncertainty and in effect favor “false negatives” and that the precautionary principle simply is more open in acknowledging its value preferences (Stirling, 2008). In addition, proponents note various regulatory failures that are based on the deterministic use of uncertain science, such as the mad cow disease epidemic in the mid-1990s in Europe that resulted in serious public-health and economic harm (Millstone et al., 2015), and they argue for a more precautionary policy.

Other commentators have noted that risk assessment and the precautionary principle may not be as irreconcilable as they are often portrayed (EC, 2000; Stirling, 2008; Driesen, 2013). The process of risk assessment itself often involves science-policy choices, such as the selection from among various plausible models for estimating risk, that involve explicit decisions to be “conservative,” that is, to err on the side of overestimating risk (NRC, 1994). In the risk-management phase that follows risk assessment, regulators must intentionally decide on the appropriate level of protection to be achieved, given statutory requirements and other considerations. Some U.S. laws have a precautionary approach, including the food-safety and pesticide-residue provisions of the Federal Food, Drug and Cosmetics Act, which require exposures to be set at levels that ensure a “reasonable certainty of no harm.” In addition, as part of risk management, U.S. federal regulators can set maximum exposure levels that reflect substantial margins of safety, particularly when there is scientific uncertainty in the risk assessment. For example, the U.S. Environmental Protection Agency is required by the Food Quality Protection Act of 1996 to use an additional 10-fold margin of safety in setting pesticide-residue tolerances to protect infants and children.

Either approach can result in regulations of similar rigor. Despite perceptions that the precautionary principle has led Europe to become more stringent than the United States in some health, safety, and environmental regulations (Vogel, 2012), one recent comprehensive analysis that compared U.S. and EU health, safety, and environmental regulations concluded that Europe has been more precautionary about some risks and the United States has been more precautionary about other risks and that overall both have maintained a rough parity of all risks over the last four decades (Hammit et al., 2013).

In contrast with the WTO agreements, the Biosafety Protocol, an international environmental agreement rather than a trade agreement, explicitly permits countries to include socioeconomic issues in their LMO biosafety risk assessment in Article 26.1.[8] The article has been subject to conflicting interpretations (Horna et al., 2013). In addition to protecting biological

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[8] Article 26.1 of the Cartagena Protocol on Biosafety states that: “The Parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of living modified organisms on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities.”

diversity and human health under the Biosafety Protocol, countries could potentially consider economic effects on farmers or even ethical or religious issues.

Although some international agreements allow the consideration of socioeconomic issues, none require it; trade agreements generally discourage it. As a result, most of the consideration of socioeconomic issues related to GE crops has been at the national level.

National Approaches

Within the overall framework of the various international agreements, national governments have crafted formal regulatory approaches for GE foods and crops that differ in several important ways. First, definitions of the kinds of crops and foods that are subject to regulation vary from country to country. In some cases, a product's regulation depends on the use of a defined genetic-engineering process; in other cases, products are regulated on the basis of the risk posed by a product's intended use or characteristics. Second, one way to characterize national regulatory systems is by their approach to genetic engineering, ranging from promotional to preventive (Table 9-1; Paarlberg, 2000; see also Chapter 3 section "Different Policy Approaches to Genetically Engineered Crops and Food"). Third, some national regulatory systems address only biosafety concerns (food safety and environmental protection), whereas others go beyond biosafety considerations to address socioeconomic concerns, such as consumer right-to-know and protection of farmers of non-GE crops from unintended gene flow from GE crops. Fourth, regulatory schemes differ in how they allocate decisions between scientific experts and political bodies that reflect broader societal views (see Munch, 1995; Klinke and Renn, 2002; Renn and Benighaus, 2013).

However, there are also similarities in various national regulatory approaches. Following the standards of such international bodies as the Codex Alimentarius Commission, the elements of the scientific risk-assessment

TABLE 9-1 The Paarlberg Model of Policy Options and Regimes Towards Genetically Engineered (GE) Crops

	Promotional	Permissive	Precautionary	Preventive
Intellectual-property rights	Full patent protection, plus PBR[a] under UPOV[b] 1991	PBR under UPOV 1991	PBR under UPOV 1978, which preserves farmers' privilege	No IPR[c] for plants or animals or IPR on paper that are not enforced

TABLE 9-1 Continued

	Promotional	Permissive	Precautionary	Preventive
Biosafety	No careful screening, only token screening, or approval based on approvals in other countries	Case-by-case screening primarily for demonstrated risk, depending on intended use of product	Case-by-case screening also for scientific uncertainties owing to novelty of genetic-engineering process	No careful case-by-case screening; risk assumed because of genetic-engineering process
Trade	GE crops promoted to lower commodity production costs and boost exports; no restrictions on imports of GE seeds or plant materials	GE crops neither promoted nor prevented; imports of GE commodities limited in same way as non-GE commodities in accordance with science-based World Trade Organization standards	Imports of GE seeds and materials screened or restrained separately and more tightly than non-GE seeds and materials; labeling requirements imposed on import of GE foods or commodities	GE seed and plant imports blocked; GE-free status maintained in hopes of capturing export market premiums
Food and human health safety and consumer choice	No regulatory distinction drawn between GE and non-GE products in either testing or labeling for product safety	Distinction made between GE and non-GE products on some existing product labels but not so as to require segregation of market channels	Comprehensive labeling of all GE products required and enforced with segregated market channels	GE product sales banned or warning labels that stigmatize GE products as unsafe to consumers required
Public research investment	Treasury resources spent on both development and local adaptations of GE crop technologies	Treasury resources spent on local adaptations of GE crop technologies but not on development of new transgenes	No substantial treasury resources spent on either GE crop research or adaptation; donors allowed to finance local adaptations of GE crops	Neither treasury nor donor funds spent on any adaptation or development of GE crop technology

[a] Plant breeders' rights.

[b] International Union for the Protection of New Varieties of Plants Convention.

[c] Intellectual-property rights.

SOURCE: Migone and Howlett (2009).

process for food safety and for environmental protection are similar among national regulatory systems.

The section reviews three national approaches and one regional approach for assessing and managing the risks associated with GE crops and foods for food safety and health, environmental effects, and socioeconomic concerns.

United States

U.S. regulatory policy for GE products, including crops and foods, was set out in the 1986 Coordinated Framework for the Regulation of Biotechnology (hereafter referred to as the Coordinated Framework). The Coordinated Framework directed U.S. regulatory agencies to use their existing legal authorities to review the safety of products created with genetic

BOX 9-3
The U.S. Coordinated Framework for the Regulation of Biotechnology

The Coordinated Framework established the basic U.S. policy for regulating biotechnology products (OSTP, 1986). It states that biotechnology products are regulated under existing federal laws in the same manner as similar products made by using conventional breeding and sets out the principal responsibilities of U.S. regulatory agencies. The White House Office of Science and Technology Policy (OSTP) found that existing laws would be sufficient to deal with expected products (OSTP, 1986:23304):

> The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens.

At the same time, OSTP recognized that technology developments could change this approach (OSTP, 1986:23306):

> Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there always can be potential problems and deficiencies in the regulatory apparatus in a fast moving field.

In 1992, OSTP provided further policy guidance that agencies shall not regulate products intended for use in the environment (such as crops) on the basis of the process by which they were made, but rather on the "characteristics of the engineering in the same manner as similar products produced by using conventional breeding (Box 9-3). As a result, how a particular product is regulated depends on its intended use (that is, as a food, drug, or pesticide) or characteristics (that is, as a plant pest). Depending on the characteristics and intended use of a GE product, more than one agency can be involved in a review of a GE crop or a food derived from a GE crop. A maize plant (*Zea mays*) engineered to express pesticidal proteins is reviewed by all three regulatory agencies: the U.S. Food and Drug Administration (FDA) for food safety, the U.S. Department of Agriculture (USDA) for plant-pest characteristics and other adverse environment effects, and the U.S. Environmental Protection Agency (EPA) to ensure that the plant-expressed pesticide does not pose unreasonable risks to human health or the environment (Figure 9-1).

organism, the target environment, and the type of application" (OSTP, 1992:6755). In making that policy determination, OSTP relied on the 1989 National Research Council report *Field Testing Genetically Modified Organisms: Framework for Decisions*, highlighting in particular its finding that "no new or inherently different hazards are associated with molecular techniques" (NRC, 1989:70).

As a result, in the United States, biotechnology products are regulated on the basis of their characteristics and intended use under law and regulations that, in theory, apply equally to similar products developed by conventional breeding. In practice, however, the U.S. regulatory system is not purely product-based; it makes distinctions on the basis of the method used to develop a new crop variety. For example, EPA exempts from the registration process new crop varieties that have been developed to have greater pest resistance through conventional-breeding technologies, including mutagenesis (40 CFR §174.25). EPA justifies that distinction on the basis that sexually compatible, conventionally bred plants are less likely to pose novel exposures of the environment than GE varieties and are therefore likely to pose less environmental risk (EPA, 2001b).

Similarly, USDA's Animal and Plant Health Inspection Service (APHIS) regulations apply only to new crop varieties that have been genetically engineered with known plant-pest sequences or using a plant as a transformation vector, such as the crown gall disease pathogen *Agrobacterium tumefaciens*. APHIS does not conduct a premarket environmental review for novel crop varieties created through conventional breeding, including crop varieties created through chemical or radiation mutagenesis or other advanced breeding techniques. In part, that policy was justified on the basis of the long history of the safe introduction of new crop varieties by plant breeders. In addition, USDA has legal authority to address only plant-pest and noxious-weed risks; it has no authority over novel traits. Genetic-engineering technology has become more advanced and plant-pest sequences are no longer needed as part of the engineering process, so some GE crops do not fall within APHIS's jurisdiction.

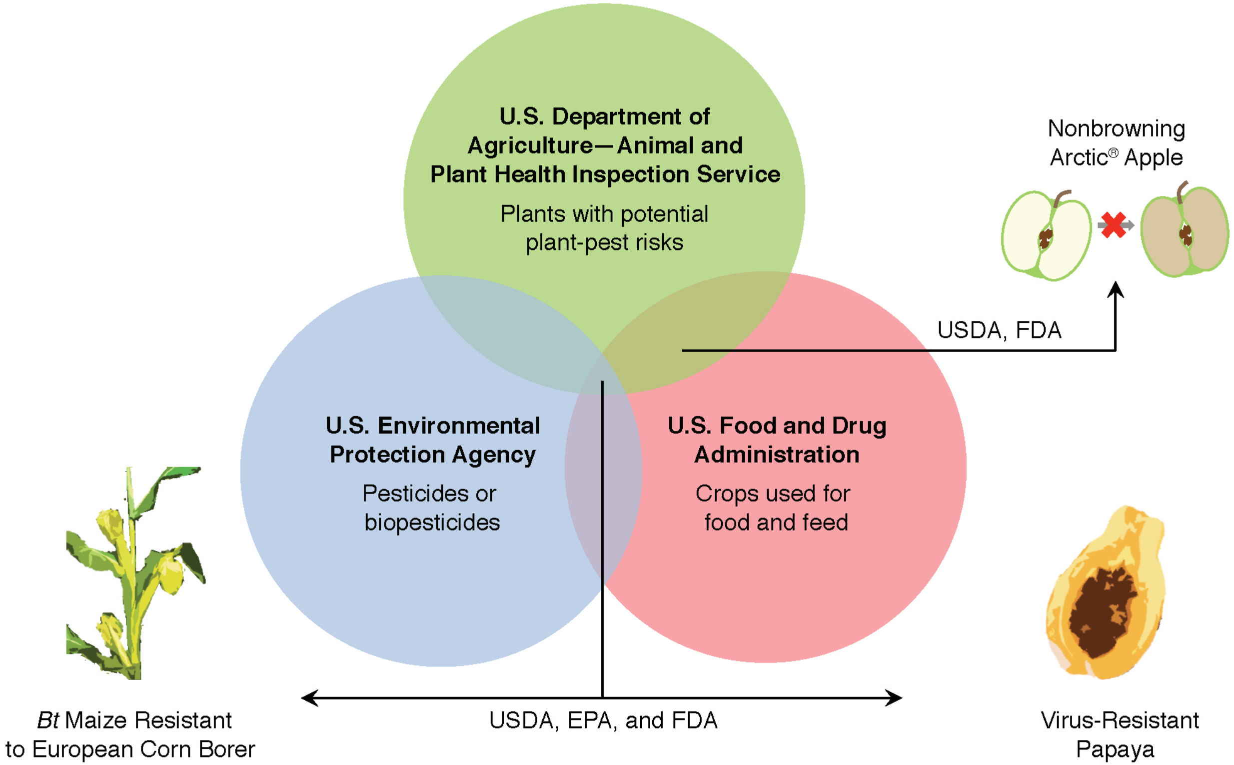

FIGURE 9-1 U.S. regulatory agencies and their responsibilities in regulating genetically engineered crops.
SOURCE: Based on Turner (2014).

Food-Safety Policy for Genetically Engineered Foods. FDA uses its food-safety authority under the Federal Food, Drug, and Cosmetic Act (FFDCA, 21 U.S.C. §301 *et seq*) to oversee the safety of foods, including foods derived from GE crops. Unlike drugs, new whole foods are not required to be approved as safe by FDA before they are introduced into the U.S. market. The responsibility for ensuring that a food is safe falls on its manufacturer. If a serious food-safety threat arises after a product is on the market, FDA has authority to recall or seize the product. Historically, novel whole-food varieties developed from conventional breeding have gone directly to market without prior government oversight. FDA notes that the practices used by plant breeders in selecting and developing new varieties of plants have historically "been proven to be reliable for ensuring food safety," and FDA has therefore not found it necessary to routinely conduct premarket safety reviews of whole foods derived from new plants based on the long record of safe development of such plants (FDA, 1992).

In 1992, FDA issued a policy statement for foods derived from GE crops stating that a whole food derived from a GE crop that was substantially equivalent to its conventionally bred counterpart would be presumed to be as safe as the conventionally bred variety (FDA, 1992). FDA stated that most GE proteins or other GE substances added to a food were likely to be similar to substances already in the food supply and therefore would presumptively be "generally recognized as safe" (GRAS).

In its policy statement, FDA left the door open for the possibility that future food products derived by genetic engineering could differ substantially from their non-GE counterparts or contain new substances that would not be GRAS. In such cases, FDA has the option to consider novel substances in a food to be "food additives," which are regulated differently from whole foods. Food additives are substances intentionally added to foods (for example, chemical preservatives) and must be approved by FDA as safe before marketing unless they are GRAS. In 1994, the FLAVR SAVR™ tomato was the first whole food from a genetically engineered plant to be reviewed by FDA under its voluntary consultation process. At the same time, at the developer's request, FDA approved an enzyme (aminoglycoside 3′ phosphotransferase II) encoded by the kanamycin resistance gene in the FLAVR SAVR tomato as a food additive (FDA, 1994).

Like novel whole foods developed through conventional breeding, most foods derived from novel GE crop varieties are not required to be reviewed or approved for safety before going to market. However, FDA has encouraged GE crop developers to consult with FDA voluntarily before going to market and to share with the agency information that the company believes demonstrates that the GE food is substantially equivalent and that any added substances are safe. The consultation process also gives FDA the opportunity to determine whether an intentionally added substance would be a food additive that would require premarket approval. FDA does not make any safety findings, but it does close the consultation process with a letter stating that FDA has no further questions and reminding the developer of its responsibility to ensure product safety. Through March 2016, FDA has completed 171 consultations (FDA, 2015a). As a practical matter, for marketing purposes, developers have stated to the committee that they view the consultation process as a de facto requirement. FDA has stated that no GE foods that have been evaluated under its voluntary consultation process have gone to market until all FDA safety questions have been resolved.[9] In 2001, FDA proposed making the consultation process mandatory, but this proposal was never made final (FDA, 2001).

Under Section 408(c) of the FFDCA, EPA has the responsibility of setting safe tolerances for pesticide residues in food. EPA must set the tolerance at a point that there is a "reasonable certainty of no harm."

Environmental Policy for Genetically Engineered Crops. Under the Coordinated Framework, both EPA and USDA's Animal and Plant Health Inspection Service (APHIS) have responsibility for assessing and managing the potential environmental risks posed by some GE crops. Given its general authority to regulate pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 7 U.S.C. §135 *et seq*), EPA has responsibility for approving pesticidal proteins expressed in GE crops (EPA, 2001b). Developers of such pest-resistant plants may not field-test them on more than 10 acres without prior EPA approval and may not release them commercially until EPA has approved them as posing no "unreasonable adverse effects on the environment."[10]

APHIS regulates some GE plants under the Plant Protection Act (7 U.S.C. §7758(c)), which generally authorizes the agency to control and prevent the spread of plant pests and noxious weeds. Under its plant pest legal authority, APHIS requires developers of plants that have been genetically engineered by using plant-pest sequences to notify APHIS or to

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[9] Questions & Answers on Food from Genetically Engineered Plants. Available at http://www.fda.gov/food/foodscienceresearch/geplants/ucm346030.htm. Accessed November 30, 2015.

[10] FIFRA defines unreasonable adverse effects on the environment as "(1) any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from the use of a pesticide in or on any food inconsistent with the standard under section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a)" (7 U.S.C. §136(bb)).

obtain a permit before any field testing or environmental release.[11] Before commercialization of a GE crop, developers typically seek a "nonregulated status" determination from APHIS, which allows them to grow the crop on a commercial scale without further regulation.[12]

In some cases, both EPA and APHIS are involved in reviewing a GE crop. For example, both EPA and APHIS review pest-resistant varieties of plants or crops for the risks addressed by their specific legal authority. Although APHIS reviews herbicide-resistant GE crops, EPA's role is limited to regulating a herbicide that will be applied to a crop (see Chapter 5 section "Regulatory Testing of Crops Resistant to Glyphosate and 2,4-D and of the New Uses of the Herbicides Themselves" for a detailed example).

EPA and APHIS both impose requirements intended to prevent the movement of transgenes from experimental field trials for the GE crops under their jurisdiction. These controls are particularly important because neither the food-safety risks nor the environmental risks associated with GE crops undergoing field trials have been assessed by a regulatory agency. Despite the restrictions on field trials, there have been numerous discoveries of low levels of unapproved GE events in seed, food, and crops (see section "Coexistence" in Chapter 6).

Once a transgenic event in a particular crop species is deregulated by APHIS, there is no further oversight from the agency because in effect the action is a determination that the plant is not within APHIS's legal authority to regulate. Consequently, USDA has not required post-approval herbicide-resistance management plans. In addition, a deregulated transgenic event may be stacked with other deregulated events if they have been previously approved for a specific crop species without further regulatory oversight by APHIS. For example, once deregulated, GE glyphosate or glufosinate resistance may be stacked in maize with other events without the need for further approval by the agency.

In contrast with APHIS, EPA requires pesticide registrants to report

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[11] APHIS's regulations were initially issued in 1987 (USDA–APHIS, 1987) and have since been amended. APHIS's rule applies to a *regulated article*, which is defined as (7 CFR §340.1):

> Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in § 340.2 of this part and meets the definition of plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the Deputy Administrator determines is a plant pest or has reason to believe is a plant pest.

[12] Under APHIS's regulations, a party may petition USDA for a determination that its plant does not pose a plant-pest risk and therefore should be deregulated. This is also referred to as a Petition for Determination of Nonregulated Status (7 CFR §340.6).

adverse events[13] (that is, unexpected potentially harmful effects) and may also require specific post-market monitoring requirements to ensure that the use of products remains consistent with FIFRA's legal standards. For example, the planting of *Bt* insect-resistant crops often requires planting of non-GE refuges near GE crops as part of an insect resistance management (IRM) strategy (EPA, 1988). The planting requirements depend on the specific protein responsible for the *Bt* trait, the crop, and the area of the country where the crop is being grown (EPA, 2001c, 2015; Smith and Smith, 2013). The strategy was introduced to reduce the selection pressure for the evolution of insects resistant to *Bt* (see Chapter 4). EPA also requires the reregistration of *Bt* crops and has adjusted the IRM strategy (EPA, 2001a, 2015; Glaser and Matten, 2003). The agency requires annual compliance reporting from the companies that sell the *Bt* crops. EPA has also restricted planting of *Bt* cotton in areas where wild cotton grows to prevent the flow of the transgene to wild cotton strains. In 2014, for the first time, EPA required a herbicide-resistance plan as part of a registration for a herbicide to be used with a GE herbicide-resistant crop.[14]

Socioeconomic Issues. U.S. laws differ markedly in the extent to which they permit or require a regulatory agency to consider economic or other nonsafety issues in making a regulatory decision. For example, under the food-additive provisions of the FFDCA, FDA can approve a food additive only when it finds it to be safe (defined in the law as "reasonable certainty of no harm"). Food must be safe; FDA cannot consider any other factors, including costs. (The same legal standard applies to EPA's tolerances for pesticide residues in food.)

In contrast, EPA is required by some laws to consider factors other than environmental harm, including economic benefits and costs. For example, FIFRA requires EPA to take into account "the economic, social, and environmental costs and benefits of the use of any pesticide" in making a decision as to whether a pesticide would have an "unreasonable adverse effect on the environment" (7 U.S.C. 136(bb)). The standard of "unreasonableness" recognizes that some magnitude of risk is acceptable as long as it is outweighed by countervailing benefits. More generally, proposed regula-

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[13] FIFRA §6(a)2. In 2001, for example, EPA conducted a reassessment of registered *Bt* maize products in light of concerns about potential adverse effects on monarch butterflies and required additional data from the registrants (EPA, 2001a).

[14] As part of the registration for Enlist Duo® herbicide—a combination of 2,4-D and glyphosate for use on herbicide-resistant maize and soybean—EPA required the developer, Dow Agrosciences, to monitor drift issues related to the use of the herbicides and to implement a herbicide resistance management (HRM) plan (EPA, 2014a). When the committee was writing its report, glyphosate was undergoing reregistration, and EPA was reportedly considering requiring an HRM as part of any approval (Gillam, 2015; Housenger, 2015).

tions are reviewed by the Office of Management and Budget to ensure that the economic and other benefits of a proposed rule outweigh its costs (Executive Office of the President, 2011).

The National Environmental Policy Act (NEPA) requires agencies to undertake a broad assessment of the effects of significant agency actions, including the consideration of the "ecological, aesthetic, cultural, economic, social, or health" effects (40 CFR §1508.8).[15] However, although agencies must go through this assessment process, NEPA does not give agencies any additional legal authority to make decisions on the basis of those factors. When APHIS deregulates a GE crop, for example, it must conduct an environmental assessment or provide an environmental impact statement to comply with NEPA, but it legally is required to deregulate a GE crop if it is not a plant pest, regardless of the outcome of the NEPA analysis. If the NEPA assessment showed an adverse ecological effect of a GE plant (for example, on air or water quality) that was not a plant-pest risk in the view of APHIS, the plant would still have to be deregulated.

U.S. regulatory agency product approvals are usually represented solely as technical decisions that a product meets the appropriate statutory requirements of safety or efficacy. Agencies generally do not consider, for example, the moral implications of a new product or the fairness of the economic effects on various stakeholders of those decisions. At least in theory, the basic approach of U.S. regulatory policy is to leave such contentious issues to public opinion, various actors, and the marketplace to sort out.

Given this general policy orientation, it is not surprising that U.S. product regulatory agencies have had limited responses to socioeconomic issues, such as consumer right-to-know and effects from GE crop gene flow on non-GE farmers. With regard to mandatory labeling of GE foods, FDA's position is that it has no legal basis under its general authority to mandate GE labeling. Section 201(n) of FFDCA prohibits food labels from being "false or misleading," which is defined as a failure "to reveal facts that are material in light of representations made or suggested in the labeling, or material with respect to consequences that may result from the use of the food to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual." Under this authority, FDA has required labeling of a number of food processes that change the character of the food (including taste, smell, and texture) that consumers might otherwise be unaware of at the time of sale, such as whether a juice drink has been made from concentrate (21 CFR 102.33(g)). FDA has concluded, however, that as a class there is no "meaningful" difference between a food produced from a GE crop and

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[15] EPA is exempt from the procedural requirements of NEPA because its actions are presumed to be consistent with the goals of NEPA.

a conventionally bred crop and that therefore there is no basis to require the disclosure of the use of genetic engineering (FDA 2001, 2015b).[16] The fact that consumers may be interested in that information is not sufficient legal grounds to mandate labeling under the FFDCA. FDA's GE labeling policy was upheld by the court in *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166 (D.D.C. 2000).

Similarly, neither EPA nor APHIS addresses the economic conflicts that arise from the coexistence of commercial GE and non-GE crops as part of the regulatory-approval process. Neither agency requires post-approval monitoring nor management plans to prevent the low-level presence of GE traits in non-GE crops or foods.[17]

At the same time, U.S. policy-makers clearly have the authority and ability to respond to social, ethical, and economic concerns through means other than product regulation. The U.S. Congress could address such issues through legislation. Executive branch agencies also have authority outside the product-regulation framework to address some of the concerns. Within USDA, for example, the Agricultural Marketing Service has a long history of working to establish marketing standards, and the secretary of agriculture has made efforts to address coexistence issues through crop insurance and other programs (USDA Advisory Committee, 2012). The Federal Trade Commission and the U.S. Department of Justice have the authority under anti-trust laws to investigate market-distortion issues that might arise from a concentrated seed industry.

Food-Safety and Environmental Risk Assessments. This section looks in more detail at how the United States uses risk assessment to characterize the food-safety and environmental risks of GE crops and foods as part of the product-approval process. The risk assessment determines the kind and quality of data that a developer must supply to the regulatory agencies.

The FDA voluntary consultation process with developers focuses on two major issues as part of the food-safety assessment: the compositional similarity of a whole food to the comparable conventionally bred variety and the safety of any substances intentionally or unintentionally added to the food through the genetic-engineering process. Analysis follows closely the Codex risk-assessment principles and guidelines, discussed above. The

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[16] The U.S. Congress has passed laws that have required specific food labels that go beyond FDA's generic legal authority; the most well-known example is nutrition labeling, which was required by Congress in the 1990 Nutrition Labeling and Education Act (P.L. 101-535).

[17] In APHIS's draft environmental assessment of Dow AgroScience's Enlist™ maize, it rejected an option to require isolation distances between GE and non-GE varieties as being "inconsistent" with its statutory authority because it had found that the GE maize was not a plant pest (USDA–APHIS, 2011:48).

FDA and EPA food-safety risk assessment processes are discussed in detail in Chapter 5.

With regard to environmental risk assessment, APHIS's regulations (7 CFR §340.6) outline the types of studies that are necessary to support a determination of nonregulated status; in effect, data are required that would enable APHIS to determine that a plant is not a "plant pest" within its legal authority. APHIS considers, among other things, whether the GE crop is more likely than its non-GE comparator to become invasive or weedy, to be more susceptible to pests or diseases, or to have greater effects on nontarget organisms. APHIS also considers the potential effects of gene flow to wild relatives and other organisms. In effect, APHIS uses the risk-assessment process to determine whether a GE crop is likely to pose a greater "plant pest" risk than a comparable conventionally bred crop variety.

To accompany its permits and deregulation decisions, APHIS is also required to prepare an environmental assessment (EA) or an environmental impact statement (EIS) in compliance with NEPA. The NEPA analysis requires APHIS to consider broader potential environmental effects than whether a plant is a plant pest, as is described above. Although APHIS does not use the non-pest plant aspects of the NEPA analysis as a basis for its decisions, it requires developers to submit data to assess environmental effects.

In its review of a pesticide registration for human health and environmental effects, EPA has not formally published data requirements for plant-incorporated protectants, but the types of studies typically required by EPA for pesticide registration have been set out in regulations (40 CFR 158) and include characterization of introduced genetic material and its expression, a suite of nontarget-organism acute-toxicity studies (mammals, aquatic species, avian species, and beneficial insects), and various environmental-fate studies. Unlike APHIS, EPA does not have to prepare an EA or EIS for its regulatory decisions under NEPA, but its broader environmental risk assessment would cover the same issues as would be required by an EA.

As technology has improved, testing capabilities have expanded, and safety questions around GE varieties have arisen, the number and types of tests that are included in a preapproval package have increased. For example, at the time the committee was writing its report, EPA was in the process of developing possible new data requirements for RNA-interference technology (RNAi) (EPA, 2014b). The list in Table 9-2 provides an example of increasing testing demands required by EPA between 1995 and 2008 for a safety assessment of a new GE variety that incorporates a pesticide.

TABLE 9-2 Safety Assessments Required for Registration of Crops Containing Plant-Incorporated Protectants by the U.S. Environmental Protection Agency (EPA), 1995 and 2008[a]

Data Category	*Bt*[b] Potato 1995	*Bt* Maize 2008
Product Characterization		
Identification of the transformation event	X	X
Identification of PIP[c] components	X	X
Spectrum of pesticidal activity		X
Mode of action	X	X
Certification of limits		X
Characterization of inserted DNA	X	X
Characterization of protein(s) – Efficacy		X
Characterization of protein(s) – Expression levels	X	X
Characterization of protein(s) – Physiochemical	X	X
Demonstration of protein equivalency	X	X
Human Health		
Mouse acute oral toxicity	X	X
Toxins – Protein database analysis		X
Allergenicity – Stability to heat, SGF,[d] SIF[e]		X
Allergenicity – Bioinformatics database analysis		X
Environmental – Nontarget Organisms		
Avian acute oral toxicity (quail/duck)	X	X
Avian dietary toxicity (broiler/duck)		
Freshwater fish toxicity		X
Freshwater invertebrate toxicity		X
Estuarine and marine animal toxicity		X
Honeybee toxicity – Larva and adult	X	X
Beneficial insect toxicity – Predators	X	X
Beneficial insect toxicity – Parasitic wasp	X	X
Non-arthropod invertebrate toxicity – Earthworm		X
Synergistic effects from multiple PIPs		X
Environmental – Environmental Fate		
Soil degradation rate	X	X

TABLE 9-2 Continued

Data Category	***Bt***[b] **Potato 1995**	***Bt* Maize 2008**
Resistance Management Data Requirements		
Target organism susceptibility		X
Simulation models		X
Potential for cross resistance		X
Resistance monitoring plan		X
Remedial action plan		X
Compliance assurance/grower education		X
Conditions of Registration		
Annual report on compliance assurance program		X
Annual report on grower education		X
Annual report on IRM[f] monitoring		X
Annual sales report		X
Other		
Analytical detection method		X
Public interest document		X

[a] This table includes the information that EPA typically requests from an applicant before the agency will grant commercial approval for a crop containing a plant-incorporated protectant (PIP). Every new registration application does not necessarily contain information for all of the categories listed. For example, *Bt* maize products that contain both previously registered *Bt* seeds and non-*Bt* seeds, known as Refuge in a Bag (RIB), require a new registration. However, EPA does not require a new data submission on effects on nontarget organisms for RIB applicants because that information was provided in the previous application. Applications to register stacks of previously registered events may also refer to elements in data packages submitted earlier. Finally, the table refers to information that accompanies a registration application. Developers of PIP-containing crops must also submit applications, with accompanying data and other forms of information to conduct field trials larger than 10 acres and for EPA either to grant a tolerance exemption or to set a food tolerance for the *Bt* protein if it is produced by a food or feed crop. That information is publicly available in EPA's decision documents, the Biopesticide Registration Action Documents. A table of current and previous registrations for PIPS is available at http://www2.epa.gov/ingredients-used-pesticide-products/current-previously-registered-section-3-plant-incorporated. Accessed December 15, 2015.

[b] Contains a gene or genes from the bacterium *Bacillus thuringiensis* (*Bt*).

[c] PIP = plant-incorporated protectant

[d] SGF = simulated gastric fluid

[e] SIF = simulated intestinal fluid

[f] IRM = integrated resistance management

SOURCE: Compiled by the Biotechnology Industry Organization Science and Regulatory Working Group in March 2012.

European Union

As a regional government, the EU's approach to regulation obviously differs from that of the United States because it is not based on existing national laws. It has taken a more precautionary approach to approving the commercialization of GE crops.

Safety of Foods Derived from Genetically Engineered Crops and Cultivation of Genetically Engineered Crops. The EU, which consisted of 28 Member States when the committee was writing its report, established a regulatory process for the assessment and approval of GE foods that intentionally incorporates a precautionary approach (see Table 9-1 for a description of the precautionary approach). Assessment and approval are triggered by the presence of a process used to introduce a trait into an organism. Under EU rules, organisms in which the genetic material has been modified in a way that "does not occur naturally by mating and/or natural recombination" are subject to mandatory premarket assessment. Included in that definition are organisms modified through the use of recombinant-DNA technology, micro-injection, and cell fusion whose result is a combination of genetic materials that do not occur naturally. The definition does not include in vitro fertilization, polyploidy induction, selective breeding, crossing, or mutagenesis (Directive 2001/18/EC Annex I A). As a result, new varieties of crops developed through conventional breeding may be introduced into the market without premarket regulatory review and approval. Once a new food from a conventionally bred crop is on the market, the EU and the Member States have the authority to recall it if health or safety issues arise under the General Food Law Regulation.

The procedures for evaluation and approval of a market application for what the EU defines as a *genetically modified organism* (GMO) are set out in Regulation (EC) No. 1829/2003 on genetically modified food and feed and in Directive 2001/18/EC on the release of GMOs into the environment.[18] Under those regulations, the European Food Safety Authority (EFSA), in cooperation with the scientific agencies of Member States, is responsible for making a food-safety and environmental assessment for all applications for GMOs to be used for cultivation, importation, or processing. The centralization of the risk-assessment process provides a "single-door" approach that applies a uniform-risk evaluation process throughout the EU.

EFSA's role is limited to providing scientific advice. Once EFSA has delivered its opinion on the food-safety and environmental-safety risks associated with an application, the decision to authorize the application,

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[18] Because *genetically modified organism* is a defined term under EU law, this section of the report uses it and such related terms as *genetically modified* (*GM*) rather than *genetically engineered organism* and *GE*.

whether for cultivation or for the marketing of food or feed without cultivation, is decided by the European Commission and the Member States. The decision process is complex and inherently has a political component, given the need for broad agreement by all the Member States (Figure 9-2). Within 3 months after receiving an EFSA opinion finding that a product does not pose a risk to health or the environment under proposed conditions of use, the Commission makes an initial draft decision. If the Commission proposes to approve the application, its draft decision is then submitted to the Member States, represented in the Standing Committee, for a vote under qualified majority rules.[19] If the Standing Committee approves, the Commission adopts the draft approval decision. If the Standing Committee votes no or fails to reach a decision within 90 days, the Commission may resubmit its draft decision to the Appeal Committee. The Member States then vote again on the Commission's draft decision in the Appeal Committee. Again, if the Member States vote yes with a qualified majority, the Commission adopts the decision. If they vote no, the Commission cannot adopt the proposal. However, as of December 2015, in all cases with respect to Commission draft approvals for GM cultivation or for food and feed, the Member States had failed to reach any decision by a qualified majority vote; there were insufficient votes either to approve or to reject. EU procedures dictate that under such circumstances the Commission is required to adopt and implement its own decision (EC, 2015c). As the Commission has explained, "the reasons invoked by Member States to justify their abstentions or negative votes are sometimes scientific in nature, but in the majority of cases are based on other considerations, reflecting the societal debate in their country" (EC, 2015c).

Given the strong public opposition to GM foods in some Member States, it has been difficult for the EU decision-making process to reach agreements to approve GM food and crop applications even when EFSA's risk assessments have concluded that a GM food or crop is as safe as non-GM counterparts. Despite the 2006 WTO dispute-settlement body's decision that the EU's failure to approve GE food or crop applications was a de facto moratorium in violation of the TBT Agreement (see above section "International Frameworks"), the EU has continued to find it difficult to approve GMO applications. As of June 2015, according to the European Commission, only one crop—Monsanto's MON810, a maize variety with a *Bt* gene to protect against the European corn borer (*Ostrinia nubilalis*)—is

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[19] The "qualified majority" decision-making process for GMO approvals is the same general process used in all EU legislative decision-making under Regulation (EC) No 182/2011 (comitology procedure). Under EU voting rules, a qualified majority consists of 55 percent of the Member States (in the case of a Commission proposal) and representing 65 percent of the population. A minority of four Member States can block a proposal (EC, 2015c).

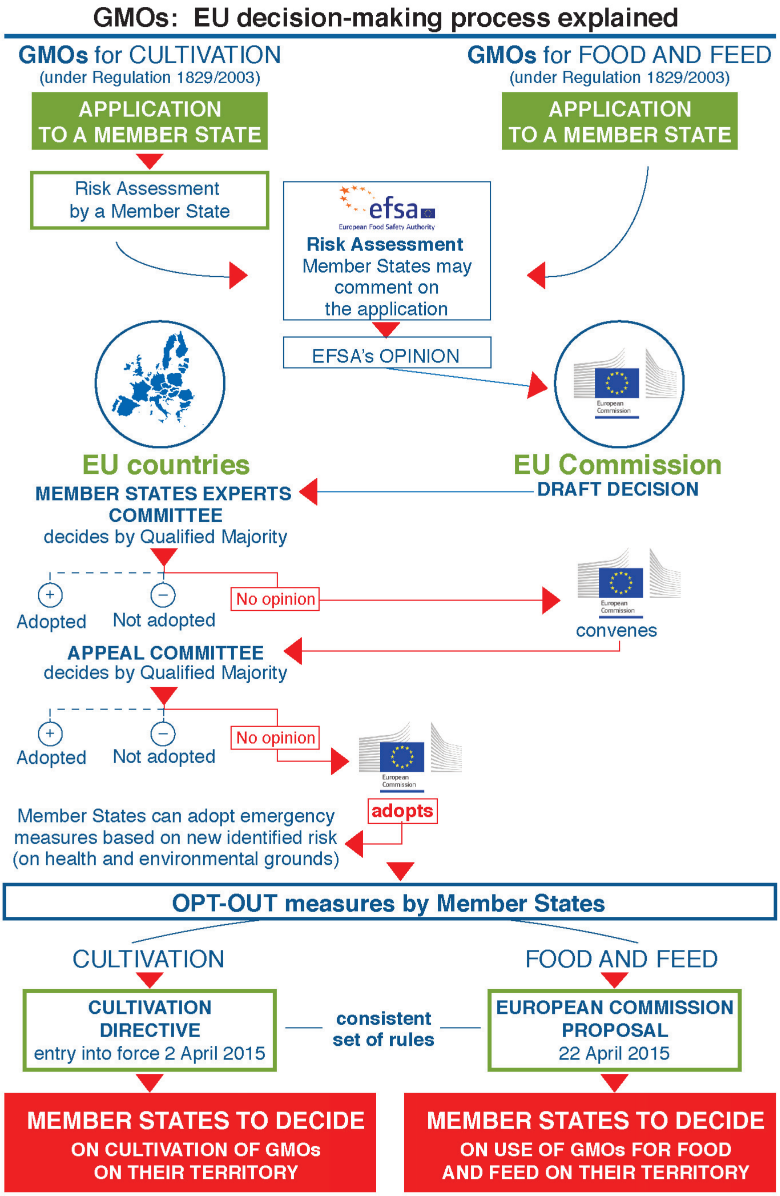

FIGURE 9-2 Roles of Member States, the European Food Safety Authority, and the European Commission in assessing the risk posed by genetically modified organisms. SOURCE: GMOs: EU decision-making process explained. Available at http://ec.europa.eu/food/plant/docs/decision_making_process.pdf. Accessed December 15, 2015.

authorized to be cultivated in the EU, and it was awaiting reauthorization.[20] At that time, MON810 was grown in five Member States; Spain accounted for most of the planted hectares, and the variety represented less than 2 percent of the total EU hectares planted to maize. Eight applications for GMO cultivation are pending, four of which have been assessed by EFSA as safe and four of which are awaiting an EFSA opinion (EC, 2015b).

The EU has approved a greater number of applications for the importation of GE food and feed than for cultivation. As of April 2015, the EU had approved 10 new GE crops, to bring the total to 68 GMOs that are authorized in the EU for food and feed purposes, including maize, cotton (*Gossypium* spp.), soybean (*Glycine max*), canola (*Brassica napus*), and sugar beet (*Beta vulgaris*) (EC, 2015a,b). The great bulk of those GMO imports are in the form of soybean feed for the EU's livestock sector, which depends heavily on imports. Few, if any, GM food products are available for sale. Most food manufacturers have reformulated their products in Europe to avoid having to label their food as containing GMOs (Wesseler, 2014).

To break the political gridlock surrounding decisions to approve the cultivation of GM crops, the EU in late 2014 adopted new rules to allow Member States to prohibit or restrict the cultivation of an approved GM crop on the basis of nonrisk policy considerations such as environmental or agricultural policy objectives, land-use planning, socioeconomic effects, or coexistence management (Directive EU 2015/412). Although the new rule clearly undercuts the desire to have a consistent and uniform policy in all EU Member States, it will allow Member States that want to grow new GM crops to proceed.

Socioeconomic Issues. The EU has adopted rules that require a GM food, feed, or grain to be labeled. The EU justifies labeling as a right-to-know issue, a right conferred in the European constitution and by international human-rights laws. When it was adopted, EU officials also stated that labeling was required partly to rebuild public confidence in its food-safety system (EC, 2001).

As discussed in Chapter 6 (Box 6-5), the EU has also developed general guidance for managing coexistence between GM and non-GM producers, although the management of coexistence has primarily been left to the Member State level. A number of Member States have adopted requirements that have largely had the effect of protecting non-GM producers.

Food-Safety and Environmental Risk Assessments. EFSA has published its risk-assessment guidelines for both food safety and the environment (EFSA, 2010, 2011b). EFSA's food-safety risk assessment, like those of

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[20] MON810 was initially authorized for use within the EU in 1998.

the Codex guidelines and FDA, starts with the comparison of the GM crop with its conventionally bred counterpart. Information provided by the applicant must include a molecular characterization, which provides information on the structure and expression of the inserted material and on the stability of the intended trait, a toxicological assessment that addresses effects of biologically relevant changes in the GM crop or food on human and animal health, an assessment of potential allergenicity of any novel protein and the whole food, and a nutritional assessment to ensure that food or feed derived from the GM crop is not nutritionally disadvantageous to humans or animals. EFSA guidelines set out the requirements for testing the toxicity of new expressed proteins. Until 2013, the EFSA guidelines did not require animal-feeding studies to test the safety of a whole food unless its composition was substantially different from its non-GM counterpart or there were other indications of unintended effects from a comparative analysis.[21] The final risk characterization should demonstrate that the consumption of a food or feed derived from a GM plant is at least as safe as its conventionally bred counterpart and that it is at least as nutritious for humans and animals as a non-GM food or feed.

Before a GM crop can be grown in the EU, an applicant has to submit a data package to enable a Member State to conduct a comprehensive environmental risk assessment (ERA). EFSA has issued guidance on the types of information that applicants must submit and the process that must be followed for an ERA (EFSA, 2010). EFSA also conducts an ERA for the whole EU territory, taking into account the Member State's ERA and any additional information EFSA may request. The ERA guidelines include seven specific concerns:

- Persistence and invasiveness of the GM crop.
- Plant-to-microorganism gene transfer.
- Interaction of the plant with target organisms.
- Interaction of the plant with nontarget organisms.
- Effects of cultivation, management, and harvesting techniques.
- Effects on biogeochemical processes.
- Effects on human and animal health.

The ERA consists of a full risk assessment, moving through the steps of problem formulation, hazard characterization, exposure characterization, and risk characterization. If risks need to be mitigated, assessment requires the applicant to propose measures for reducing them to a level of "no con-

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[21] As noted in Chapter 5, EU regulations adopted in 2013 require EFSA to conduct whole-food rodent feeding studies as part of its risk assessment (Implementing Regulation (EU) 503/203). EFSA has issued guidance on animal-feeding studies (EFSA, 2014).

cern." EFSA, like its USDA and EPA counterparts, often asks for additional information from the applicant to supplement the original application.

Each application for cultivation also requires a post-market environmental monitoring (PMEM) plan under which the applicant will continue to monitor for potential adverse environmental effects (EFSA, 2011a). PMEM plans are also required for any live GE material (grain or seeds) imported into the EU market.

In preparing risk assessments, EFSA works with scientific bodies in the Member States, including a network of over 100 organizations and authorities in Europe. Member States are given an opportunity to provide input to the EFSA GMO assessments. With its final opinion, EFSA also publishes a summary of the comments and input from Member States.

Canada

Canada takes yet a different approach to regulation. Its system uses the concept of "novelty" in assessing whether there is a need to regulate new crops, regardless of the breeding method used.

Genetically Engineered Crops and Foods. Like the United States, Canada has divided the regulatory responsibilities for GE foods and crops. Health Canada is the agency responsible for food safety in the Canadian regulatory system, and the Canadian Food Inspection Agency (CFIA) is responsible for assessing the environmental effects of new crops.

Unlike the United States, Canada passed new laws to revise its regulatory system to address concerns being raised about GE crops and foods. However, the new laws reflected a policy of focusing on novel foods and novel plant traits rather than on a specific breeding process (genetic engineering) or product category (such as plant pests).[22] Thus, the Canadian regulatory system appears to follow a process-neutral approach in determining which foods and plants should be subject to mandatory premarket government review. Instead of focusing on the intended uses or characteristics of a plant or the use of a specific process, the Canadian approach centers on risk: the potential for novel food or environmental exposures.

Consequently, Division 28 of the Food and Drugs Regulation, also referred to as the Novel Foods Regulation, establishes a premarket notification process for all "novel foods," whether GE or not. "Novel foods"

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[22] Canada's regulatory framework followed 7 years of discussions with stakeholders (Smyth and McHughen, 2012). Early field trials in the 1980s and early 1990s were held under the authority of existing laws, primarily the Seeds Act (1985), the Feeds Act (1983), and the Food and Drugs Act (1985) (Smyth and McHughen, 2012). Regulations implementing the "novel foods" and plants with "novel traits" approaches were first issued by CFIA in 1994.

can be summarized as products that do not have a history of safe use as food, foods that have been subjected to a process that has not previously been used for them and that causes them to undergo a major change, and foods derived from plants or animals that have been genetically modified to introduce or delete traits or to change the anticipated array of characteristics (B.28.001 C.R.C., c. 870 (2014)). The term *genetically modify* is defined as to change "the heritable traits of a plant, animal, or microorganism" (B.28.001). In an on-line posting of frequently asked questions, Health Canada has indicated that "genetic modification" is not limited to recombinant-DNA technologies but could also include conventional breeding, mutagenesis, and emerging genetic-engineering technologies, such as genome editing (Health Canada, 2015).[23] That definition includes only a subset of "new" foods; in particular, developers or importers of foods that have been safely used in other countries or that have only minor processing changes are not required to submit prior notification (Smyth and McHughen, 2012).

Developers and importers of a "novel food" must notify Health Canada at least 45 days before its marketing and submit information sufficient to demonstrate its safety. Health Canada may request additional information; once satisfied that the food is safe, Health Canada notifies the submitter in writing that the information is sufficient and that the agency has "no objection" to its marketing in Canada. No "novel food" may be marketed before receiving authorization from Health Canada. The agency publishes a summary of the notification and its decision on-line.

According to information on the Health Canada website, over 81 GE foods and many more non-GE foods were assessed and approved as novel foods for sale in Canada as of 2015. Non-GE foods include an artificial sweetener (Sucromalt), foods treated with a novel high-pressure process for sanitation, foods with added ingredients (such as phytosterols), and novel non-GE food varieties, including herbicide-resistant sunflower (*Helianthus annuus*) and mid-oleic sunflower oil. Once a food is approved, there is no requirement for routine post-approval food-safety monitoring, although developers and food manufacturers must report any new adverse safety information.

Environmental risks posed by crops are the responsibility of CFIA, which assesses the environmental safety of plants and the safety of animal feed under the Seeds Act and the Feeds Act. Developers of a plant with "novel traits" (PNT) must obtain authorization from CFIA before conducting confined field trials or unconfined release (including commercialization). A "novel trait" is one that is new to stable, cultivated populations

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[23] On its website, Health Canada uses the terms *genetically modified* and *genetically engineered* interchangeably. In the discussion in this section, *genetically engineered* (or *GE*) is used.

of the plant species in Canada and that has a potential to have a substantial adverse environmental effect (CFIA, 2009). When the committee was writing its report, all GE plants reviewed by CFIA had been considered to contain novel traits. However, as mentioned above, novel traits can also be introduced through non-GE techniques. For example, in 2005, CFIA reviewed and approved BASF Canada's CLEARFIELD® sunflower, which has a novel trait for resistance to the herbicide imidazolinone (CFIA, 2005). The trait originated in a natural mutation in the wild sunflower population in Kansas and was introduced into domestic germplasm by conventional breeding. CFIA has also reviewed and approved BASF Canada's CLEARFIELD imidazolinone-resistant trait in canola and wheat (*Triticum aestivum*) (CFIA, 2007, 2008); in these cases, the traits were introduced through chemically induced seed mutagenesis and interspecific crossing.

So far, all GE crops have been submitted by their developers for regulatory review, but not all future GE crops are expected to have novel traits (Thomas and Yarrow, 2012). Once a PNT has been introduced into the environment, its trait may no longer be considered novel in the Canadian approach. As a result, a later plant of the same species transformed with the same DNA construct and expressing the same traits as an approved variety should not be subject to the full regulatory-approval process (Smyth and McHughen, 2012). In addition, in some cases the developer of a crop with stacked traits, each of which has already been approved, would not have to submit the full regulatory-approval package (CFIA, 1994). In practice, however, developers of varieties stacked with previously approved traits have continued to submit them for full regulatory approval (Thomas and Yarrow, 2012). Furthermore, new crop varieties that confer insect resistance or herbicide resistance will still need to have stewardship plans for managing resistance development even if the traits were already approved. If a plant is no longer a PNT, it may still be a novel food that will require approval by Health Canada.

In the Canadian system, it is the responsibility of the plant breeder to make the initial determination of whether a plant has novel traits. CFIA has issued guidelines to help plant breeders to determine both whether a plant is "new" to the environment and whether it has the potential for environmental harm (CFIA, 2009). A trait will not be considered "new" if it has been observed in a population of the same species cultivated in Canada. Simply increasing the frequency of the trait would not be sufficient for a trait to be considered new, but a trait could be considered new if it is expressed at levels substantially outside observed ranges. In most conventional plant breeding, new varieties display relatively small changes in trait expression that are unlikely to require regulatory review. CFIA has acknowledged that in most cases products of conventional plant breeding are unlikely to pose a risk to the environment. However, the concept of novelty provides regulatory flexibility and adaptability to cover new crop varieties that pose greater risk, regardless of the method by which they were produced. At the same time, the novelty trigger is somewhat less predictable than a clearly determinable process-based trigger. For that reason, CFIA encourages plant breeders to come in for early consultation during the development process.

Socioeconomic Issues. Canada's regulatory approach is more similar to the market-oriented approach of the United States than to the social-welfare approach of the EU (Marcoux and Létourneau, 2013). Like the United States, Canada does not require labeling of GE foods. The Canadian government participated in a multistakeholder process with the Canadian Council of Grocery Distributors and the Canadian General Standards Board to develop a standard to guide the use of voluntary labeling to ensure that it is truthful and not misleading. The Standard for Voluntary Labeling and Advertising of Foods that Are and Are Not Products of Genetic Engineering was published as a national standard of Canada in 2004 (Canadian General Standards Board, 2004).

Also like the United States, Canada does not regulate coexistence between GE and non-GE producers (Dessureault and Lupescu, 2014) and, as in the United States, the consequence is that the economic burden of avoiding gene drift and commingling is on the producers of non-GE crops. According to USDA's Foreign Agriculture Service, however, there is not enough information to determine the extent of unwanted admixture of GE crops and organic crops and the damage entailed (Dessureault and Lupescu, 2014).

The Canadian system includes one aspect that serves socioeconomic ends. Under the Seeds Act, any new variety of a major agricultural crop—whether GE or not—has to receive prior approval from CFIA's Variety Registration Office after review by an advisory committee with representatives from public and private institutions that examines the new crop variety to ensure that it is at least equal in quality to existing varieties. That approval process is intended to protect Canadian farmers from inferior new crop varieties and to ensure that the new varieties will deliver the benefits as described. However, the office's focus is on the quality of the new variety, not on the possible economic consequences of its introduction (Smyth and McHughen, 2012).

Food-Safety and Environmental Risk Assessments. Health Canada has published guidelines for the safety assessment of novel foods, detailing the information to be submitted by food manufacturers or importers. The guidelines were derived from the food-safety assessments developed by the OECD, the Food and Agriculture Organization, the World Health Organization, and the Codex Alimentarius Commission (Health Canada, 1994, amended 2006). A food-safety assessment examines how a food crop was developed, including molecular biological data, the composition and nutritional profile of the novel food compared with non-GE counterpart foods, the potential to introduce new toxins or to cause allergic reactions, and dietary exposure by the average consumer and by sensitive populations, such as children. Health Canada estimates that it typically takes 7–10 years of product development for a company to compile enough data to submit a premarket notification for a novel food (Health Canada, 2015).

Environmental risk assessments are conducted by CFIA. In considering whether a plant meets the environmental-risk part of the novel-trait definition, CFIA focuses on whether a new variety is likely to have a more adverse environmental effect than its non-GE counterpart. Adverse effects to be considered include weediness potential, harmful gene flow, plant-pest potential, effects on nontarget organisms, and other potential adverse effects on biodiversity (CFIA, 2009).

Before any PNT is grown in a confined field trial, the applicant must apply for approval from CFIA and submit a data package with information on the crop variety and the description of the field trial. An authorization for a confined research field trial is subject to general and crop-specific terms and conditions, which are intended to minimize persistence and spread of the plant in the environment and prevent contamination of feed and food with unapproved plant material. Enforcement of those terms and conditions by CFIA involves site inspections during the growing season and post-harvest monitoring (CFIA, 2000). After approval, nonconfidential information about confined research field trials is posted on CFIA's website.

When field trials have been completed and developers want to commercialize the PNT, developers must apply to CFIA for approval for an unconfined environmental release. Applicants must submit a data package that will permit CFIA to complete a thorough environmental-safety assessment (CFIA, 1994). CFIA compares the environmental effects of the new variety with those of a non-GE counterpart to ensure that it poses no greater environmental risk than the counterpart. CFIA may impose restrictions to manage or mitigate adverse environmental effects. In addition, CFIA requires stewardship plans for herbicide-resistant or insect-resistant crops to prevent the development of resistance and prolong the lifespan and usefulness of the technology. Developers are also expected to implement a post-release monitoring plan for unintended or unexpected environmental effects. Applicants are required to report any adverse information on environmental effects. As with approvals for confined field trials, decisions to approve unconfined environmental releases are posted on CFIA's website, as are documents explaining the decision reached by CFIA.

Brazil

Unlike the other governments reviewed here, Brazil's government adopted a regulatory policy when GE crops were already being grown in the country. Economic and environmental concerns played a role in when and what kind of system was put into place.

Food-Safety and Environmental Policy for Genetically Engineered Crops. Brazil's regulatory scheme for GE foods and crops became law in 2005. Brazil passed its first law for GE foods and crops in 1995, but the law generated protest and controversy after the National Technical Commission of Biosafety (CTNBio) approved a request for the commercial release of a glyphosate-resistant soybean without requiring the completion of an environmental impact report. CTNBio's authority was challenged in court by the Institute of Consumer Defense and Greenpeace as violating environmental laws.

A lower court issued an injunction against CTNBio's approval, and the case was taken to a three-judge appeals court, which delayed a decision for several years while there were extensive and often contentious discussions among Brazilian civil-society groups, farmers, biotechnology companies, and government officials (Soares, 2014) about how GE-food and GE-crop approval decisions should be made and who should make them (Schnepf, 2003; Cardoso et al., 2005). Issues related to the roles of democratic decision-making, scientific expertise, the equitable distribution of risks and benefits, and potential effects on the environment and biodiversity were all elements of the debate. In 2003, the controversy was exacerbated by news that substantial amounts of GE soybean seeds had been smuggled from Argentina and illegally planted in parts of southern Brazil and had become commingled with non-GE soybean (Schnepf, 2003). At the time, USDA estimated that 10–20 percent of Brazil's total soybean crop might have consisted of illegally planted GE soybean varieties (Schnepf, 2003).

In 2003, after two temporary authorizations of the GE soybeans that were already planted and harvested in 2003 and after extended negotiations, new legislation was proposed. The new biosafety framework law was passed in 2005 after long debate as Law No. 11,105.[24]

The 2005 Brazilian biosafety law established several organizations with different decision-making responsibilities for biotechnology decisions (Figure 9-3). Like the EU, Brazil has a "technical" organization that conducts risk assessments of GE foods and crops (CTNBio) and a separate political decision-making body with final decision-making authority that can weigh

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[24] Law No. 11,105 was modified in 2007 by Law No. 11,460 and in 2006 by Decree No. 5591.

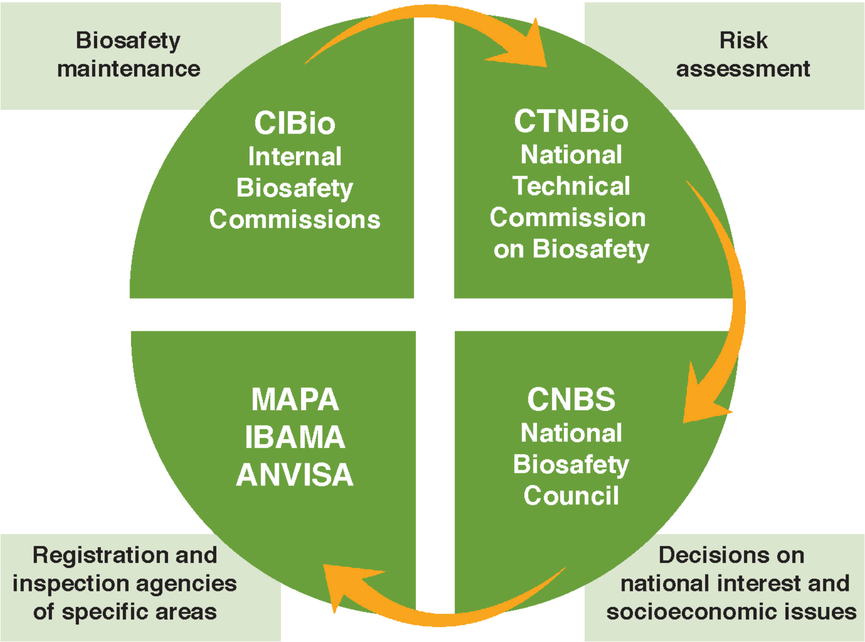

FIGURE 9-3 Structure of Brazilian regulation of genetically engineered crops.
SOURCE: Finardi Filho (2014).
NOTE: MAPA = Ministry of Agriculture, Livestock, and Food Supply; IBAMA = Brazilian Institute of Environment and Renewable Natural Resources; ANVISA = Ministry of Health through the National Surveillance Agency.

nonbiosafety issues, including socioeconomic effects: the National Biosafety Council (CNBS). Unlike the EU, however, Brazil has approved numerous GE crops for cultivation: as of 2014, more than 35 GE varieties (mostly of maize, soybean, and cotton) had been approved for commercialization under the system, and Brazil had become the world's second largest grower of GE crops.

Under Brazil's regulatory system, CTNBio is responsible for all technical issues related to biotechnology. It conducts the assessment of food-safety and environmental risks for GE foods and crops, including imports.[25]

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[25] Under Brazil's law, a *GMO* is defined as an organism whose genetic material (DNA or RNA) has been modified by "any genetic engineering" technique; *genetic engineering* is defined as the activity of manipulating DNA or RNA recombinant molecules. A *GM byproduct* is defined as a product obtained from a GMO that has no autonomous replication capacity or that does not contain a viable GM form. See Article 3 (V and VI).

CTNBio consists of 27 members, including officials in nine federal ministries, 12 technical specialists, and six other specialists in such fields as consumer rights and family farming (Silva, 2014). CTNBio was established under the Ministry of Science and Technology; its members are appointed for 2 years. A majority vote is required to recommend approvals of new biotechnology products. CTNBio's meetings are open to the public. CTNBio also authorizes all field trials in Brazil; no environmental releases may be conducted before a Certificate of Quality in Biosafety is obtained from CTNBio.

CNBS, also established by law, is in the Office of the President and is responsible for developing and implementing overall national biosafety policies. It considers broader national and socioeconomic implications of agricultural biotechnology. CNBS is a purely political body, consisting of 11 cabinet ministers. Although the 2005 Brazilian biosafety law gives CNBS the authority to make the final decision on commercialization of GE products, as the practice has evolved CNBS views the technical safety determinations by CTNBio as conclusive on biosafety issues and reconsiders CTNBio determinations only when there are issues of national interest or social or economic issues (Silva, 2014). If a socioeconomic issue is raised during the CTNBio risk-assessment process, CNBS can commission a third party to study it. In that respect, Brazil separates the technical assessment from nonbiosafety issues (Ludlow et al., 2013).

Regulation and inspection of GE crop field trials is primarily the responsibility of the Ministry of Agriculture, Livestock, and Food Supply. The Ministry of Health through the National Surveillance Agency inspects the events for toxicity, and the Ministry of the Environment through the Brazilian Institute of Environment and Renewable Natural Resources monitors and inspects the events and their effects on the environment.

After approval, CTNBio retains the authority to suspend or revoke an authorization for an environmental release of a GE crop and its byproducts if there is evidence of adverse effects on the environment or on human or animal health (Soares, 2014). In addition, CTNBio requires post-market environmental monitoring and has required specific post-market studies in several instances to address potential environmental concerns (Mendonça-Hagler et al., 2008).

Socioeconomic Issues. Brazil has adopted a number of policy measures intended to promote coexistence of farmers growing GE crops and other farmers (Soares, 2014). In 2007, CTNBio issued Normative Instruction No. 4, establishing minimum isolation distances between GE and non-GE maize crops. CTNBio has also issued coexistence rules related to the planned release of GE citrus plants (Normative Instruction No. 10) and sorghum (Normative Instruction No. 13). Exclusion zones have been required to prevent gene flow from GE cotton areas where naturally growing populations of wild cotton occur. Furthermore, no GE crops are permitted in Indian reservations or in officially recognized preservation areas (Mendonça-Hagler et al., 2008).

The Brazilian biotechnology law also establishes a general liability regime, in which persons responsible for damage to the environment or to third parties from GE crops are liable for damages regardless of any negligence on their part (Soares, 2014). The law also provides for civil and criminal penalties for violations of biotechnology regulations and rules.

In 2003, Brazil's president mandated labeling of GE foods and food ingredients for products exceeding 1.0-percent GE content. The Ministry of Justice issued implementing regulations requiring foods containing more than 1.0 percent to carry a specified transgenic logo, an uppercase "T" in a yellow triangle. In 2008, it was reported that that requirement was not being enforced (Mendonça-Hagler et al., 2008). In 2012, however, Nestlé was fined by a Brazilian court for failing to label GE soybean ingredients found in several of its consumer products (Jornal DCI, 2012).

Food-Safety and Environmental Risk Assessments. CTNBio's food-safety assessment follows the concept of substantial equivalence and the guidelines of the Codex Alimentarius Commission (Mendonça-Hagler et al., 2008).

A planned release of GE crops into the environment must initially be approved by a company's Internal Biosafety Committee. After that approval, the applicant submits a dossier for approval to CTNBio. CTNBio has issued regulations specifying the information to be included in the dossier, including information on the GE plant (a description of the modification and the process used, the exogenous DNA or RNA sequence, and genetic characteristics that may affect fitness) and information on the planned release, including protocols for safety and monitoring (Annexes I–IV of Normative Resolution No. 6). CTNBio's risk assessment evaluates the potential adverse effects of the crop and its byproducts on human and animal health, on the environment, and on plants while "maintaining transparency, the scientific method, and the precautionary principle" (Normative Resolution No. 5, Article 6(I)).

Conclusions on Comparison of Regulatory Approaches

The four regulatory regimes for agricultural products of genetic engineering reviewed above scarcely provide a comprehensive review. Rather, they are intended to present some illustrative examples of the array of policy approaches adopted in different regions. In all cases, the development of rules involved political controversy and took a substantial period to put into place. In the EU, initial regulatory approaches met opposition and were replaced with more stringent regulations and labeling requirements, and even these have been difficult to implement. Canada's rules were developed over an extensive period of consultation (Thomas and Yarrow, 2012). Brazil's initial attempt to regulate GE crops and foods in 1995 broke down in contentious disagreements. Even in the United States, where the basic policy framework was adopted in 1986, there was controversy over some aspects of agency rule-making, including EPA's proposal to regulate plant-incorporated protectants. (EPA initially proposed the rule in 1994; the final rule was published in 2001.) Regulations continue to evolve. The EU recently adopted changes to allow Member States to opt out of growing EU-approved GE crops (EC, 2015b). In 2015, the U.S. Office of Science and Technology Policy announced a comprehensive review of biotechnology regulations (OSTP, 2015), and in 2016, APHIS published proposals for revising its GE plant regulations (USDA–APHIS, 2016).

The four examples illustrate different approaches to the decision of what kinds of new foods and crops require premarket regulatory review. Both the EU and Brazil have chosen to regulate genetic engineering specifically, excluding conventional and other breeding methods. Canada has taken a different approach, choosing to regulate foods and plants on the basis of novelty and potential for harm, regardless of the breeding technique used. Unlike other countries, the United States has relied on existing product-regulation laws as the basis for regulation of GE crops and products derived from them. Although in theory the United States has adopted a product-based policy, in effect APHIS and EPA both take the breeding process into account in determining which plants to regulate.

The processes used in all four regulatory approaches to assess environmental and food-safety risks are similar and are based on guidelines and recommendations issued by the Codex Alimentarius Commission (in the case of food safety) and other international bodies, such as the OECD (in the case of environmental safety). For both food and environmental safety, the risk-assessment process used by all countries starts with the fundamental idea of comparison of a GE variety with a known, conventionally bred counterpart. Risk assessment focuses on the intended and unintended differences and considers the effects of the differences on relevant endpoints. For food, the primary issues to be considered include the potential effects of compositional changes on nutritional elements, toxicity, and allergenicity. Environmental issues include effects on nontarget organisms, changes in invasiveness or weediness, and potential for unwanted gene transfer to related species. In every case, developers are required to submit a package of data from field trials and other sources to show that the GE variety poses risks no greater than its non-GE counterpart.

Once a risk assessment has been completed, it needs to be decided whether the risk (and its uncertainty) posed by the GE variety is "acceptable" within the country's legal and cultural framework. The regulatory regimes handle that risk-management decision differently. In the United States and Canada, the decision is left to regulatory agencies that are expected to consider primarily the narrow biosafety question of whether the GE variety poses a risk substantially greater than its non-GE counterpart. Issues of socioeconomic effects are generally not addressed in the approval decision. The EU and Brazil separate risk assessment and risk management, which is handled by a government body with direct political accountability. In some cases, broader socioeconomic issues, including consumer "right-to-know" and effects on other producers, are brought into the approval decision-making process.

Those differences and conflicts are not unique. The diverse regulatory processes for products of genetic engineering mirror the broader social, legal, and cultural differences among nations. Conflicts also arise in the context of the development of international trade standards and the individual autonomy of nation-states to protect the cultural and social values specific to the countries. The United States has been a world leader in the effort to develop liberalized trade rules. Countries with stronger traditions of social welfare are not likely to be equally enthusiastic about regulatory processes that emphasize benefits of trade. As a result, the conflicts over trade discussed in Chapter 6 that arise from asynchronous product approvals are likely to continue.

FINDING: The diverse regulatory processes for products of genetic engineering mirror the broader social, political, legal, and cultural differences among countries.

FINDING: Conflicts about trade and disagreements about regulatory models are likely to continue to be a part of the international landscape.

REGULATORY IMPLICATIONS OF EMERGING GENETIC-ENGINEERING TECHNOLOGIES

As outlined in Chapter 7, the toolset of genetic engineering is changing rapidly, and new, more specific, and potentially more powerful genetic-engineering technologies are coming into use. As others have noted (Lusser et al., 2012; Lusser and Davies, 2013; Hartung and Schiemann, 2014; Voytas and Gao, 2014), the emerging technologies are likely to challenge regulatory schemes in divergent ways.

An initial issue is whether crops made with the technologies will fall within the definition of GE crops used by various regulatory agencies as a regulatory trigger and therefore be subject to premarket safety reviews. This issue is particularly relevant for regulatory systems that use a process-based definition, although the answer would need to be determined with reference to the specific language of the law.[26] Some GE plants already fall outside existing regulatory definitions (Table 9-3).

Whether that regulatory development is of concern depends on a second critical question: whether crops made with emerging genetic-engineering technologies will have risk characteristics different from plants made with other breeding techniques and, if so, what this means for regulation. Emerging genetic-engineering technologies may also pose challenges for risk assessment. Many of the current risk-assessment guidelines for GE crops are based on the assumption that the plants have been modified with transgenic recombinant-DNA technology that introduces a gene sequence from one organism into the genome of another organism through in vitro manipulation. Knowledge of the biological function and structure of the inserted gene and the donor organism is important in understanding the function of the gene in the new organism and thus a critical component of the risk assessment. Some of the emerging technologies might result in crops that at a genetic level are generally similar to crops engineered with recombinant-DNA technology, in which known DNA from one biological species is added to the genome of another species. Such cases are less likely to present novel challenges for risk assessors unless they involve gene-drive technology (see discussion in Chapter 7). However, future crop varieties could have added DNA sequences that have been computationally designed with no known biological source or could be transformed without the use of recombinant DNA. It is still unknown how, or even whether, such approaches should be regulated.

Some of the emerging genetic-engineering technologies, such as precisely targeted gene knockouts, also have the potential to create novel plant varieties that are hard to distinguish genetically from plants produced through processes that occur in nature and through conventional breeding (Voytas and Gao, 2014). The size and extent of the genetic transformation itself has relatively little relevance to its biological effect and consequently its environmental or food-safety risk. As explained in Chapter 7, small genetic changes can lead to important changes in phenotype, and large genetic changes can lead to relatively trivial changes in phenotype.

Chapter 7 describes several of the technologies for improving plant genetics that are emerging. Genome editing with meganucleases, zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced palindromic repeats (CRISPR)/Cas9

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[26] As often occurs, there may be room for disagreement about the applicability of laws and regulations. Compare, for example, the conclusion of the New Breeding Technology Platform that the EU regulations do not apply to most of the emerging technologies (NBT Platform, 2013) and an analysis by the German Federal Agency for Nature Conservation that comes to the opposite conclusion (Rehder, 2015).

nuclease system will increasingly be used in crop genetic improvement. Synthetic biology, or computationally designed genetics, has been practiced on microorganisms for the last decade but is relatively new for plants (Liu et al., 2013; Liu and Stewart, 2015). Computational design of novel genes and even genomes (Liu and Stewart, 2015) could challenge existing regulations that are process-based.

Genome Editing

Genome editing uses novel altered nucleases and complementary components to edit the sequence and function of genes in situ (Chapter 7). Plant genomes can currently be edited in three ways: a gene can be disabled (knocked out), the sequence of a functional endogenous gene can be changed, and a chromosomal locus can be targeted for the insertion of DNA precisely in that location.

That third outcome of precise transgenic insertion is probably the least problematic for existing process-based regulatory approaches. Precise gene targeting has long been a goal of plant biotechnology; genome-editing methods make precise transgene placement possible (Liu et al., 2013). The addition to a plant of genes or elements that control gene expression would probably be covered as genetic engineering under existing process-based regulatory definitions.

The cases of gene knockouts and small sequence changes are less clear (Jones, 2015). Genome-editing methods—including ZFN, TALEN, or CRISPR—can make small, precise changes or deletions in genetic sequences that can have substantial effects on a plant's phenotype. (Indeed, the CRISPR/Cas9 system is likely to be a "game-changer" in every application of biology, including in crops (Belhaj et al., 2015).)

Many process-based regulatory systems would not cover such plants despite the important alteration of the plant phenotype. For example, APHIS regulations cover only plants that retain some genetic sequences derived from a known "plant pest" in the final plant. The genome-editing methods are already creating GE plants that have no plant-pest components and are therefore not regulated by APHIS.[27] Table 9-3 shows that since 2011 APHIS has determined that many new GE events do not fall under its purview because a plant pest is not used to introduce the GE crop. It is interesting to note that when the White House Office of Science and

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[27] Cibus, a company in San Diego, California, has commercially introduced in the United States a nontransgenic herbicide-resistant canola developed by using a genome-editing technique to introduce a point mutation to endow the resistant trait. The variety appears not be regulated in the United States. Cibus plans to use similar technology to commercialize other herbicide-resistant crops, including flax and rice (www.cibus.com, accessed April 13, 2016).

TABLE 9-3 Regulated Status of Genetically Engineered Products Submitted in Letters of Inquiry to the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) for Determination of Regulation

Category	Inquiry Date	Applicant	Host Organism
I Null Segregants	1/18/2011	USDA Agricultural Research Service	Plum
	1/22/2011	North Carolina State University	Tobacco
	1/27/2011	New Zealand Institute for Plant and Food Research	N/A
	12/10/2011	University of Nebraska	Sorghum
	7/29/2013	Cellectis	Potato
	3/17/2015	Agravida	Maize
	4/28/2015	Arnold & Porter LLP	Tobacco
	8/25/2015	Calyxt	Wheat
II Gene Delivery Systems	3/8/1995	(none listed)	Carnation
	12/11/2007	New Zealand Crop and Food Limited	Petunia
	9/1/2009	Noble Foundation	Barrel medic *(Medicago truncatula)*
	9/13/2010	Scotts Company	Kentucky bluegrass
	1/20/2012	Ceres, Inc.	Switchgrass
	1/31/2012	Scotts Company	Kentucky bluegrass
	2/1/2012	Scotts Company	St. Augustinegrass
	7/23/2012	Ceres, Inc.	Switchgrass
	7/23/2012	Ceres, Inc.	Switchgrass
	7/23/2012	Ceres, Inc.	Switchgrass
	7/23/2012	Ceres, Inc.	Switchgrass
	7/30/2012	Del Monte Fresh Produce Company	Pineapple
	9/14/2012	ArborGen	Pine
	2/22/2013	Ceres	Sorghum
	3/25/2013	(CBI redacted)	*Kalanchoe blossfeldiana* and hybrids
	4/5/2013	Scotts	Tall fescue
	6/1/2013	University of Georgia	Soybean
	8/30/2013	Ceres	Maize
	10/1/2014	Glowing Plants Inc.	Arabidopsis
	1/13/2015	B.H. Biosystems	Maize
	12/14/2015	Bayer CropScience	Tobacco
III Cisgenesis and Intragenesis	2/8/2012	University of Florida	Grape
	2/23/2012	Wageningen University	Apple
IV Site-Directed Nucleases	3/1/2010	Dow	Maize
	3/2/2010	Dow	Maize
	9/9/2011	Cellectis	N/A
	9/10/2011	Cellectis	N/A
	2/7/2014	Iowa State University	Rice
	11/17/2014	Cellectis	Soy
	3/12/2015	Cellectis	Soy
V Other	3/7/1994	Washington State University	*Rhizobium leguminosarum*
	2/16/2005	V.P. Technology Development	*Chlamydomonas reinhardtii* HSV8
	4/6/2008	Coastal Biomarine	Algae strains
	2/21/2011	Danziger	Baby's Breath
	6/15/2012	BioGlow LLC	(CBI redacted)
	10/23/2012	BioGlow LLC	(CBI redacted)
	1/10/2013	Rutgers IR4 Project	N/A

*Transgenic crops modified by targeted deletions during which no plant-pest genetic information is incorporated into the host genome were determined to fall.

SOURCE: Table 1 from Camacho et al. (2014), updated by the committee with letters of inquiry to APHIS dated until April 8, 2016.

Modification / Phenotype / Product Descrption	Transformation Method	Status
Accelerated breeding	(none listed)	–
Accelerated breeding	(none listed)	–
Centromere-mediated chromosome elimination/production of doubled haploids	(none listed)	–
Decreased MSH1 Expression	*Agrobacterium tumefaciens*	–
Improved consumer & processing quality	Transient expression of TALENs	–
High starch in leaves and stalks	Meganuclease deletions	–
Accelerated breeding; 'reduced harm traits'	(none listed)	–
Improved disease resistance	Transient expression of TALENs	–
(none listed)	*Agrobacterium tumefaciens*	–
Altered vegetative pigmentation	Biolistics	–
Tnt1 retrotransposon expression (knockout library)	*Agrobacterium tumefaciens*	Regulated
Glyphosate resistant	Biolistics	–
Improved biofuel yield potential	Biolistics	–
Glyphosate resistant, enhanced turfgrass quality	Biolistics	–
Glyphosate resistant, enhanced turfgrass quality	Biolistics	–
Enhanced water-use efficiency	Biolistics	–
Biomass more easily converted to fermentable sugars	Biolistics	–
Biomass more easily converted to fermentable sugars	Biolistics	–
Biomass more easily converted to fermentable sugars	Biolistics	–
Altered fruit tissue color/anthocyanin content	*Agrobacterium tumefaciens*	–
Improved wood density	Biolistics	–
Improved biomass, juice volume & total sugars	Biolistics	–
Insertion of *rol* gene from natural isolate; compact stature	*Agrobacterium rhizogenes*	–
Glyphosate resistant & improved turfgrass quality	Biolistics	–
Altered flavonoid profiles	Biolistics	–
Improved digestibility, insecticidal properties, improved palatability, drought tolerance, increased seed yield and/or dwarfing	Biolistics	–
Bioluminescence	Biolistics	–
Improved yield (photosynthetic capacity)	Biolistics	–
improved photosynthetic capacity and biomass production	Biolistics	–
Increased anthocyanin production (intragenic)	Biolistics	–
Scab disease resistance (cisgenic)	*Agrobacterium tumefaciens*	Regulated
Suppressed phytate biosynthesis	Zinc-finger nuclease (EXZACT™)	–
Suppressed phytate biosynthesis	Zinc-finger nuclease (EXZACT™)	Regulated*
Genome editing (targeted Indels)	Meganuclease (I-Cre1) deletions	–
Genome editing (targeted Indels)	Meganuclease (I-Cre1) substitutions or additions	Regulated*
Improved disease resistance	Transient expression of TALENs	–
FAD2 knockout; improved consumer quality	Transient expression of TALENs	–
FAD3 knockout; improved consumer quality	Transient expression of TALENs	–
Insect tolerance	(none listed)	–
Expression of antibodies for human therapeutics	(none listed)	–
Expression of a glucose transporter from *Chlorella*	(none listed)	–
Altered flower color	(none listed)	–
(CBI redacted)	(CBI redacted)	–
(CBI redacted)	(CBI redacted)	–
Plasmid; conferring fus crown rot (tomato) resistance	N/A	–

NOTE: CBI = confidential business information. In the status column, "–" indicates that APHIS considers that the item in the query would not be regulated and therefore should not enter its regulatory system.

Technology Policy (OSTP) developed the Coordinated Framework in 1986, it was just a few months before the invention of GE plant production by particle bombardment became publicly known (Klein et al., 1987). Most of the applications in Table 9-3 use particle bombardment (also known as the gene gun), a nonbiological method to make GE plants (see Chapter 3). In all likelihood, at the time of adoption in 1986, OSTP and APHIS could not have foreseen GE plants not regulated by APHIS because, until that time, all GE plants had been produced using the plant pathogen *Agrobacterium tumefaciens*.

It is now possible to use molecular techniques to suppress expression of a protein or disable a protein's function without having any new DNA added to a plant. This situation mimics what could readily occur in nature or in conventional breeding (Voytas and Gao, 2014). Indeed, wheat has been genome-edited with TALENs and CRISPRs to edit the six copies of a gene in the crop simultaneously to confer resistance to powdery mildew (see Box 7-2). If similar resistance had been achieved through the insertion of genetic material from an unrelated organism, the transformed plant would fall under EPA's current regulations as a "plant-incorporated protectant." In the case of knockouts, however, the pest-resistant or virus-resistant plant contains no new genetic material from a nonsexually compatible source and is therefore likely to be exempt from EPA's registration requirements under its current rules (EPA, 2001b, §174.25).

When the committee was writing its report, most applications of genome editing had been to accomplish gene knockouts. Nevertheless, it was possible to insert DNA and change DNA bases with the new methods (reviewed in Mahfouz et al., 2014; Belhaj et al., 2015). A few changes in an endogenous plant gene can confer an agronomic trait, such as herbicide resistance.[28] Thus, small changes in gene sequence in an endogenous gene can result in large phenotype and fitness changes. These small genome edits can sometimes mimic a mutation that can occur in nature. As with knockouts, whether such edited plants would be subject to a premarket regulatory-approval process would depend on the specific wording of the regulations; they would almost certainly not be covered by APHIS despite the addition of a herbicide-resistant trait.

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[28] For example, by changing the glyphosate binding site in the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) gene by just two nucleotides, which results in changes in two amino acids, the "TIPS" (T102I + P106S) mutation will confer glyphosate resistance. Indeed, that mutation has occurred naturally in the weed Indian goosegrass (*Eleusine indica*) and endowed resistance higher by a factor of over 2,500 than the wild-type gene and higher by a factor of 600 than the single mutation (P106S) in the EPSPS gene (Yu et al., 2015). The same TIPS mutation has been rendered in the EPSPS gene in tobacco by using TALENs and would be feasible in almost any crop with any of the genome-editing approaches.

Genome editing will force a compelling dilemma for some regulatory approaches: it is now possible to change plant genetics without leaving any trace of genome-editing reagents. In several cases in which the nuclease gene has been segregated away from the site-directed mutation, genome-edited plants have no exogenous DNA (reviewed in Voytas and Gao, 2014). Genetic engineering of the epigenome (see Chapter 7) raises the same issues, inasmuch as there would be no change in the target organism's DNA.

Synthetic Genes and Genomes

The increased development of synthesized genetic components raises several regulatory issues. Whether the insertion of synthetic promoters and transcription factors into a plant would trigger regulatory review under process-based definitions will depend on the specific wording of the various regulations. Such additions would probably be covered by many process-based approaches, although the APHIS approach of covering plants that have been engineered with the use of plant-pest organisms would not seem to apply to computationally derived sequences. Synthetic DNA sequences with no direct biological species analogue would not fall within the current APHIS regulations, in which the biological source of recombinant DNA plays an important role. In the case of new genome-editing reagents, U.S. regulatory agencies are not structured to regulate the DNA-free delivery of a reagent that produces a targeted mutation but leaves no exogenous DNA footprint with the host genome (see Chapter 7). Indeed, in late 2015, the Swedish Board of Agriculture deemed transgenic *Arabidopsis* that was genome-edited via CRISPR not subject to regulations and started allowing field tests. The nontransgenic and DNA-free delivery of CRISPR would be even more likely to be exempt from regulation under the Swedish approach because it would not have a transgene.

For risk assessment, synthetic components also raise issues. On the one hand, because the sequences will be not derived from a biological source, they may have no direct analogue or comparator in nature, which could result in additional regulatory uncertainty. On the other hand, a synthetic promoter would probably be streamlined and have more precise function than endogenous promoters (Liu and Stewart, 2016). For example, a synthetic promoter, such as a soybean cyst nematode-inducible promoter designed for expression in soybean roots, is about one-tenth the length of the typical plant promoter and has been computationally designed not to have any cryptic transcriptional start sites or any other issues that could lead to off-target regulation of gene expression (Liu et al., 2014). Therefore, risk potential might actually be decreased by use of some synthetic components.

With the ability to design genes and genetic control elements computationally and with the relatively inexpensive DNA synthesis and assembly methods that are routinely available (Kosuri and Church, 2014), entire synthetic organelle genomes can be built. Yeast (*Saccharomyces cerevisiae*) synthetic chromosomes have been built and installed into the genome to replace their endogenous counterparts (Annaluru et al., 2014). Although yeast has a more streamlined nuclear genome than plants, such design features will probably find their way into plants. Indeed, a 150,000–base-pair synthetic chloroplast genome (plastome) is already feasible to design, manufacture, and install into plants (Liu and Stewart, 2015).

A plant with a synthetic plastome would pose a challenge for risk assessments because it might lack a known natural biological comparator, the basis of present substantial-equivalence risk-assessment paradigms. Furthermore, the gene-by-gene regulatory paradigm of incremental improvement could be severely challenged by synthetic genomes or subgenomes in which many genes and traits are changed simultaneously.

RELATED REGULATORY ISSUES

The regulatory process in most countries for current and future GE crops addresses primarily the biosafety of the products. However, additional issues are related to the products, such as coexistence, labeling, post-approval environmental monitoring, and public participation. Here, the committee looks at how regulation may interact with commercialized products and with GE products that may be developed in the future with emerging technologies.

The Role of Product Regulation Beyond Biosafety

As noted above, some countries use their product regulatory systems to address socioeconomic and other policy issues that go beyond the mission of ensuring the safety of food and other products. In the case of GE foods and crops, the two primary issues that emerge are managing coexistence of GE, non-GE, and organic-farm production systems and mandatory labeling of GE foods.

Those issues clearly involve social and economic choices that go beyond scientific assessments of health or environmental safety; ultimately, they inherently involve value choices that science alone cannot answer. It is likely that different societies will balance the competing interests in different ways.

As noted above, product regulation in the United States is primarily viewed as a technical process that does not incorporate broader ethical concerns or issues about the fairness to stakeholders into product-approval decisions. That regulatory approach reflects fundamental cultural values, including respect for the marketplace and a limited role for government, that may differ in other countries.

That observation does not mean, however, that the issues cannot be addressed by U.S. policy-makers and the private sector as a broader part of technology governance. Outside the product regulation process, the U.S. Congress has addressed a number of economic, ethical, and social concerns, such as animal welfare, protections for research subjects, crop insurance, marketing standards, and voluntary labeling programs. Such issues can also be addressed by nongovernmental actions, including voluntary standard-setting organizations.

On the issue of coexistence, Chapter 6 notes that nonregulatory parts of USDA (such as the Agricultural Marketing Service and the Federal Grain Inspection Service) have a long history of working with the private sector to ensure orderly markets and trade and could address coexistence issues. The secretary of agriculture has also made efforts to address coexistence through the Advisory Committee on 21st Century Agriculture and various workshops. The private sector is playing a major role in developing markets that put together producers and consumers by managing supply chains and contractual obligations. When the committee's report was being written, the various governance efforts had not been sufficient to address the concerns raised by organic growers and growers of non-GE crops or to meet the need to protect identity-preserved channels for various GE crops that have not received full export approvals. As noted in Chapter 6, the risk of adventitious presence currently affects producers of non-GE crops in the United States.

Mandatory labeling is a similarly complex issue that involves competing values. There clearly are strong nonsafety arguments and considerable public support for mandatory labeling of products containing GE material. On the basis of its review of the evidence on health effects (Chapter 5), the committee does not believe that mandatory labeling of foods with GE content is justified to protect public health. As discussed in more detail later in the present chapter, previous reports from the National Research Council have consistently upheld the view that the process by which a food is made or a crop is bred is a poor indicator of risk. All technologies for improving plant genetics have the potential to change foods in ways that raise safety issues.

As discussed in Chapter 6, however, product labeling serves purposes that go beyond food safety. As with coexistence, U.S. policy-makers and the private sector have the ability to address the broader social and economic issues and to balance the competing interests involved. The marketplace is also responding to consumer interest in avoiding GE foods: the number of products voluntarily labeled as “non-GMO” has increased dramatically in the last 10 years.[29]

> **FINDING: Policy regarding GE crops has scientific, legal, and social dimensions, and not all issues can be answered by science alone. Indeed, conclusions about GE crops often depend on how stakeholders and decision-makers set priorities among and weigh different considerations and values.**

> **RECOMMENDATION: 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.**

The Role of Expertise, Public Participation, and Transparency in Product Regulation

Different countries allocate the roles of risk assessment and risk-management decisions in different ways. In the examples included in this report, every country has a technical expert body to conduct a risk assessment of a product seeking regulatory approval. The risk assessment provides a scientifically based evaluation of a product’s overall food-safety and environmental risks. The decision of whether to approve a product for commercialization or to approve it with conditions needed to prevent or mitigate potential harm is the risk-management decision. Depending on the particular law involved, the approval process may take into account such issues as costs, benefits, and socioeconomic effects. For that reason, some countries have chosen to give the risk-management decision to bodies that are more politically accountable and that can reflect public opinion. In the EU, for example, approvals of GE crops and foods involve the representatives of Member States; in Brazil, final approvals are the responsibility of a group of cabinet ministers. In the United States and Canada, the same agency that conducts the risk assessment is also responsible for making

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[29] There is no national standard for “non-GE” claims, and FDA has provided guidance for voluntary labeling to ensure that such labels are not misleading (FDA, 2015b). One large voluntary certification and labeling program is operated by the Non-GMO Project, under which foods that are certified to follow the Project’s standards may include the “Non-GMO Project Verified” label on the package (www.nongmoproject.org). The Project states that it has participation from 1,500 brands accounting for more than $11 billion in annual sales. Recently, USDA approved the use of a USDA “Non-GMO/GE Process Verified” label for one food company (NGFA, 2015). Other “non-GE” labels are evolving in the U.S. marketplace (Strom, 2015).

the product-approval decision. Because the approval decision is seen to be more narrowly based on the question of safety as determined by the risk assessment, the U.S. and Canadian approaches give final approval authority to agencies that are more insulated from political and public influences.

The approaches discussed above all attempt to address the tension between expertise and democratic accountability experienced in different contexts (Liberatore and Funtowicz, 2003) in a climate in which some members of the public are growing more and more distrustful of elite experts (Fisher, 2009). Inclusionary approaches are not always successful. For example, Hatanaka and Konefal (2013) described a process in which a participatory approach was attempted to establish the legitimacy and integrity of a sustainability standard. Legitimacy has three interrelated elements: input, procedural, and output. It is assumed generally that there is a positive relationship between the three, that is, legitimacy of any one contributes to the legitimacy of the others. However, it is possible that input legitimacy can contribute to weakened procedural and output legitimacy (Tamm Hallström and Boström, 2010; Hatanaka and Konefal, 2013). Hatanaka and Konefal found that the sustainability standard lacked output legitimacy because too many actors with differing opinions on input watered down the standard during its creation and key actors opted out of the process during contentious negotiations. In another example, Endres (2005) reported a similar outcome related to an effort to create a coexistence working group. The group reached consensus (and near unanimity) on relevant "best management practices" to foster coexistence among organic, non-GE, and GE crop production. However, after initial voting on the proposed best management practices, five members of the group withdrew their support and discontinued participation in the project (Endres, 2005). That withdrawal, despite input legitimacy, led to a failure of output legitimacy.

Despite such failures, institutions (including the National Academy of Sciences and the National Research Council) have responded to the concerns about trust and democratic legitimacy primarily through changes in process to expand transparency and public participation. Many efforts have been made to find innovative ways to include the public in decision-making on issues involving technical or scientific matters (Rowe and Frewer, 2005).

As noted in Chapter 2, international human-rights law protects rights to access to information and public participation and requires that exceptions to these rights be drawn as narrowly as possible. National Research Council committees have long recognized the need for transparency and robust public participation, both generally regarding risk analysis of scientific issues and specifically regarding GE crops. The 1996 National Research Council report discussed in Chapter 2, *Understanding Risk: Informing Decisions in a Democratic Society*, noted the importance of including stakeholder participation throughout the risk-assessment process and particularly during the final phase of risk characterization (NRC, 1996:11):

> Risk characterization involves complex, value-laden judgments and a need for effective dialogue between technical experts and interested and affected citizens who may lack technical expertise, yet have essential information and often hold strong views and substantial power in our democratic society.

The report noted that risk characterization benefits as much from deliberation with stakeholders as from expert analysis. The process should involve "sufficiently diverse participation from across the spectrum of interested and affected parties to ensure that the important, decision-relevant knowledge enters the process, that the important perspectives are considered, and that the parties' legitimate concerns about the inclusiveness and openness of the process are addressed" (NRC, 1996:4).

Another National Research Council report, *Science and Decisions: Advancing Risk Assessment*, offered similar recommendations, urging greater public inclusion in the risk-assessment process, particularly in the early stages of problem formulation, not only to improve public acceptance of the analysis but to improve the analysis for the purposes of risk management (NRC, 2009). Public communication and inclusion are particularly important with respect to emerging genetic-engineering technologies, including areas such as synthetic biology, and prospective regulatory methodologies, such as the use of -omics technologies. Institutions involved in regulating GE crops thus should pay special attention to communicating with the public about and seeking public input regarding how those institutions might regulate emerging technologies and their products and how they might use -omics technologies.

The issues involved in policies regarding genetic engineering are complex and require the input of many stakeholders, particularly as new technologies and new applications are considered (Oye et al., 2014). The importance of transparency and public participation in the risk assessment of GE crops in particular was emphasized in the 2002 National Research Council report *Environmental Effects of Transgenic Plants*. In assessing environmental risks, including stakeholders and the public is important because there is less consensus about what constitutes an environmental risk—what is worth protecting (NRC, 2002). The committee found that "public confidence in biotechnology will require that socioeconomic impacts are evaluated along with environmental risks and that people representing diverse values have an opportunity to participate in judgments about the impact of the technology" (NRC, 2002:245).

The present committee did not have adequate information on the regulatory-approval processes of other countries to make an informed judgment about the adequacy of transparency and the opportunity for public participation during risk assessment and risk management. However, it was aware of a number of efforts in the EU and elsewhere to engage stakeholders and publics on the issue of GE crops and foods outside the formal product-approval process (Medlock et al., 2007).

In the United States, transparency and opportunities for stakeholder and public participation in regulatory-agency product-approval proceedings are constrained by laws that protect confidential business information and define how and when agencies may communicate with the public, particularly the Freedom of Information Act, which provides the overarching framework for transparency regarding government actions, and the Administrative Procedures Act, which provides rules for public participation in rule-making. Agencies have made commendable efforts to post more of their proposed actions and decisions on-line to make it easier for the public to be aware of or to comment on specific actions. Furthermore, agencies have attempted to create opportunities for discussion with stakeholders and the public beyond the "notice-and-comment" procedure required for agency rule-making. In 2015, APHIS suspended a rule-making proceeding to provide an opportunity for a more flexible engagement with stakeholders and the public on its biotechnology regulations (USDA–APHIS, 2015).

Nevertheless, opportunities for public engagement in an agency decision-making process are limited, and much information submitted to an agency in support of a product approval remains protected as confidential business information. In particular, the committee was aware that the lack of public access to the health and safety data submitted by developers creates distrust in some stakeholders.[30] Although agencies publish a summary of their decisions based on the data, the public cannot judge for itself the quality, objectivity, and comprehensiveness of the materials submitted. Given a developer's self-interest in getting a product approved and its control over the material considered by the agency, the lack of access creates skepticism about the quality of the data. To address that concern, EFSA was planning to make industry data submissions publicly available over the next few years (Rabesandratana, 2015). Some stakeholders have commented on the need for increased GE crop safety research funding for academic scientists not funded by the biotechnology industry to provide peer-reviewed

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[30] With respect to FDA's consultation process, interested parties are able to obtain the developer submissions and related data that are not trade secrets or confidential commercial information from the agency by submitting a Freedom of Information Act request. Health and safety data submitted to FDA as part of final consultations are typically available to the public upon request.

and publicly accessible information. In 2002, the U.S. General Accounting Office (now Government Accountability Office) recommended that FDA randomly verify raw test data that provide the basis of a developer's submission to enhance its evaluation process and improve credibility (GAO, 2002). When the committee was writing its report, FDA had not indicated whether it had adopted that suggestion.

The committee recognizes the legitimacy of the confidential nature of business information as a rationale for withholding some data from public access and understands that U.S. agencies are constrained by various laws in what they can publicly disclose. Within that framework, however, the committee concludes, on the basis of research findings, that transparency and public participation are critical and urges agencies to ensure that exemptions from disclosure are as narrow as possible. The committee also urges developers to disclose voluntarily as much of the health and safety information submitted to agencies as possible.

FINDING: Transparency and public participation have been shown by research to be critically important for appropriate, sound, and credible governance of all aspects of the development, deployment, and use of GE crops.

RECOMMENDATION: 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.

RECOMMENDATION: 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 ensure that exemptions are as narrow as possible.

Post-Approval Environmental Monitoring

Premarket regulatory safety reviews are intended to prevent harmful foods or plants from going to market. In many cases, however, regulators know that identified risks exist or are faced with uncertainty about risks. One way to manage those situations is to impose conditions on commercial use that are intended to mitigate potential harm and to require post-approval monitoring to ensure that there are no unexpected adverse events. Post-market controls and monitoring are critical risk-management tools.

Most of the national GE crop regulatory systems considered in this report routinely impose continuing requirements such as monitoring after crops have been approved. In particular, crops with herbicide-resistant or insect-resistant traits are required by most regulators to have stewardship plans in place to reduce the evolution of insect and weed resistance, including requirements to monitor for resistance and unanticipated adverse effects (see, for example, EFSA, 2010, Part 4; and EFSA, 2011a).

APHIS has taken the position that it lacks the legal authority to require post-market conditions or monitoring. Under APHIS, the final step for a typical crop is deregulation, which is in effect a decision by the agency that the crop is not a plant pest and that it therefore no longer has any legal authority to continue to regulate it. One of the consequences is that APHIS did not require developers to institute any post-approval management practices to reduce the potential for weed resistance to glyphosate, nor did it require developers to monitor for resistance or other unexpected effects. A requirement for monitoring might have prevented the rapid spread of glyphosate-resistant weeds discussed in Chapter 4. An authority to establish and enforce post-approval requirements to reduce resistance or mitigate other environmental effects is a critical tool for risk-management agencies.[31] In contrast with APHIS, as noted previously, EPA has exercised its authority under FIFRA to require post-approval monitoring and pest-resistance–management programs for *Bt* crops and more recently proposed resistance-management programs for some herbicides used with herbicide-resistant crops. Post-approval regulatory authority also enables risk managers to impose conditions on use, such as restrictions intended to reduce the potential for unwanted gene flow, when a risk assessment raises uncertainties and caution is therefore required. Similarly, post-approval monitoring could have alerted APHIS to the increasing spread of glyphosate-resistant weeds at an early stage and enabled it to make mid-course corrections.

> **RECOMMENDATION: 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.**

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[31] Post-market authority also enables regulatory agencies to work with affected stakeholders to develop and promote voluntary, community-based pest-resistance–management programs (Iowa State University, 2015).

SCOPE OF PRODUCTS SUBJECT TO PREMARKET REGULATORY SAFETY ASSESSMENT

As noted above, one continuing regulatory issue has been the question of what, if any, new crops and foods should be subject to regulatory scrutiny for safety before going to market. For regulatory efficiency, the goal of any product-regulation system should be to assess premarket safety of those products most likely to pose unacceptable risk. The practical difficulty, of course, is for the regulatory agencies to identify such products in advance while allowing safe and useful products to proceed to market.

Many countries have adopted process-based regulations that require premarket food-safety and environmental protection approvals for crops or foods that have been genetically engineered in specified ways, in part on the assumption that the engineering process or the novel traits that can be introduced by genetic engineering makes such plants more likely to be risky than new crops developed through other breeding techniques.

Previous National Research Council reports have consistently said that the breeding process used to introduce a new trait into a crop is not a particularly useful indicator of new or increased hazards. A 1989 National Research Council report noted that crops "modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits" (NRC, 1989:67). As a 2000 National Research Council report stated, "both methods have the potential to produce organisms of high or low risk" (NRC, 2000:43). In addition, National Academy of Sciences and National Research Council reports have concluded that transgenic techniques create no "unique" categories of hazards (NAS, 1987; NRC, 2000, 2002). As the 2000 report noted, "toxicity, allergenicity, effects of gene flow, development of resistant plants, and effects on non-target species are concerns for both conventional and transgenic pest-protected plants" (NRC, 2000:6). Indeed, the committee found it difficult to conceive of a totally different category of hazard that could be posed by any plant-breeding process.[32]

By focusing only on particular forms of genetic engineering, such process-based regulatory approaches may be underregulating plants developed with other breeding processes that can pose equal or greater hazards, increase exposure, or create greater uncertainty about risk. The 2004 National Research Council report *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects* found that some breeding processes, including mutagenesis, are more likely to intro-

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[32] A possible exception is gene drives in plants. When the present committee was writing its report, a different National Academies committee was investigating gene-drive research. Its report, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*, was published in 2016.

duce unintended effects (NRC, 2004) than some other breeding processes. Whether such unintended changes pose environmental or human health risks depends on the specific changes made in the plant (NRC, 2004); many unintended changes are likely to be benign.[33]

The array of emerging genetic-engineering technologies, including genome editing and synthetic biology, makes it clear that any attempt by regulators to define the scope of a regulatory system through the definition of specified technologies will be rapidly outmoded by new approaches. Many of the emerging technologies will not be covered under existing rules. Some emerging technologies could result in new plant varieties that genetically look very much like the products of conventional cross-breeding, whereas others could result in the introduction of synthetic gene sequences without a natural counterpart, creating uncertainty about potential hazard. Differentiating what is genetic engineering and what is conventional breeding is becoming more difficult.

Although the U.S. regulatory system avoids some of those issues, its emphasis on product categories creates similar issues of inconsistency for environmental risks. APHIS has authority to regulate only narrowly defined plant pests. Therefore, some plants with novel traits (such as herbicide resistance) are reviewed for plant-pest risks before being approved because they contain DNA sequences from plant pests, and other plants with similar traits that have been introduced with techniques that do not require the use of plant-pest genetic sequences may be commercialized without any APHIS regulatory review. Similarly, EPA, as a policy matter, has exempted plants with pest-resistant traits that have been introduced through conventional breeding; as a result, genome editing would most likely not be covered by EPA's current rules, although EPA is considering possible data requirements for RNAi technology (EPA, 2014b) and other genetic-engineering technologies not currently covered.

In addition, both EPA and APHIS review plants with traits that have been previously reviewed for other crops and varieties and are already in wide use. Earlier National Research Council reports have stressed that risk needs to be determined on the basis of the properties of the modified plant and the specific environment into which it is intended to be introduced. To be consistent with that approach, a more effective regulatory approach would give premarket scrutiny to plants that express traits that are new to established, cultivated crop species and that pose a potential for envi-

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[33] In addition to the unintended changes in the plant itself, risk assessors need to consider unexpected or unintended effects of the trait that has been intentionally introduced into the plant. In the environmental assessment, for example, regulators would need to consider whether organisms other than the intended target organism of a plant-incorporated protectant would be unintentionally harmed, whether through direct action (for example, toxicity) or indirect action (for example, loss of habitat).

ronmental harm, regardless of the process used. In concept, that is the approach adopted by Canada for plants with novel traits. The policy focuses appropriately on the two critical elements of risk assessment: hazard and exposure.

The introduction of a novel trait that has not previously been present in an established, cultivated crop species represents a novel exposure and therefore has an increased uncertainty of risk with respect to environmental effect. (Conversely, familiarity with a plant, trait, and the intended environment reduces the uncertainty of a risk assessment.) In contrast, a plant with a relatively small change in a trait that already exists in that environment is less likely to create environmental disruption because organisms in the environment have already been exposed to the trait and environmental responses are already established. The novelty of a trait in a crop species and the power of its expression are relevant to the exposure portion of the risk-assessment analysis.

In addition to exposure, there has to be a hazard—an agent or mechanism that causes some undesirable environmental outcome or increases a food-safety risk. For example, a new GE trait could affect the reproduction of beneficial insects when they are exposed to it in the field, or a plant might contain a protein with known potential for allergenicity.

In many cases, there may be substantial uncertainty about whether there is a hazard at all or how severe the hazard is. As technology provides plant breeders with more powerful tools, it creates the potential to introduce novel traits with which breeders and regulators have no clear comparators or experience. Such cases may be rare, but given the potential for novel exposure, it is a reasonable policy response to review such plants before their release into the environment. Risk managers can obtain additional information under field trial conditions requiring containment and other risk-mitigation measures intended to prevent uncontrolled releases.

A Tiered Approach to Premarket Regulatory Testing

An immediate concern that arises regarding regulation based on the novelty of a trait in a cultivated plant species is that there would be a broad expansion of the varieties that would undergo the full array of premarket testing because it would not be possible to exclude the possibility that an unintended change during any genetic-engineering or conventional-breeding process would lead to novel biological properties. As pointed out above, even a small genetic change could lead to biologically important alterations of a crop, so it would not be possible to exempt plants with small genetic changes.

Over the last 20 years, however, not only genetic-engineering techniques have advanced rapidly but so have other genomic methods, and some of these, called -omics technologies, enable much more accurate assessment of whether unintended biological changes have occurred in a plant that has been manipulated by conventional-breeding or genetic-engineering processes. As discussed in detail in Chapters 5 and 7, a number of -omics screening methods that can scan almost the entire DNA sequence of a plant and the quantitative profile of its messenger RNAs (mRNA) have been developed. Not quite as advanced are -omics methods for understanding and quantifying a plant's proteins, epigenome, and other molecules (metabolites), but these methods are advancing rapidly. None of these -omics methods are required by regulatory agencies, but, as reviewed in Chapter 5, they are being used by researchers to compare available GE crops with their non-GE counterparts. When those studies are conducted carefully (that is, with near-isogenic lines grown side by side with identical farming practices, appropriate replication, and good laboratory practices), the only differences in mRNA, protein, and metabolite profiles should be the ones that are intended. The studies reviewed in Chapter 5 bear that out. Other studies that compare the profiles of current GE crops with those of an array of varieties of the same crop also typically find no unexpected alterations.

In Chapter 7, the committee reviews the scientific basis of the -omics technologies and their current limitations. Although the committee emphasizes that finding a difference does not mean that there is a safety risk, not finding any unexpected differences is strong evidence that there is unlikely to be an unintended alteration that could pose a safety risk. The committee outlines research investments that could improve precision while decreasing cost of risk analyses. Most important, the committee develops a flow diagram (Figure 7-6) to explain how the -omics technologies could be used in a tiered approach to risk analysis to streamline testing of many new varieties.

The potential for adopting -omics technologies for regulatory screening purposes has been discussed in disciplines beyond food safety and environmental safety. For example, Marx-Stoelting et al. (2015) discussed the outcome of a workshop evaluating the potential future uses of -omics technologies for regulatory toxicology. Some of the limitations of -omics for regulatory toxicology are related to interpreting differences that are found because most of the compounds to be tested are expected to cause some differences. Liebsch et al. (2011) examined the potential of -omics methods for replacing some animal testing. They also saw the issue of interpreting differences as a challenge. The limitations in interpreting differences do not constitute as great a barrier for testing crops and foods because the finding of no differences is much more likely and useful in the case of crops and foods. Nevertheless, as indicated in Chapter 7, there is a need for investment in publicly accessible databases and improved methods if -omics technologies are to be used in a tiered approach with future GE and conventionally bred crops within current risk-assessment paradigms.

Alternative Policy That Eliminates Premarket Regulatory Review

The committee also considered an alternative regulatory policy that would let all new plant varieties, regardless of the methods by which they are made, go to market without premarket regulatory review and approval and allow regulators to respond if food-safety or environmental issues appear later. (Such products as drugs and pesticides would still, of course, be subject to applicable laws.) That would make plant breeders and food manufacturers primarily responsible for the safety of their products, as is the case for conventionally bred plants and foods. One could argue that the food-safety record of GE crops and foods over the last 20 years suggests that they are just as safe as conventionally bred crops and should not be subject to expensive government regulation on food-safety grounds. As noted in Chapter 6, the costs of the regulatory system can operate as a barrier to entry, particularly to public researchers, small seed companies, and specialty-crop developers that either lack financial resources or do not see the ability to recoup those costs in the marketplace. As a result, critics argue that biotechnology regulation has had the effect of keeping valuable and beneficial new crops and plants off the market and perversely benefiting large seed developers by restricting competition.

That policy option, however, has drawbacks. Although most novel crop varieties are likely to be as safe as those already on the market, some may raise legitimate concerns. As discussed above, it should be possible to distinguish among plants on the basis of their probable risk, taking into account the potential for exposure and harm. Furthermore, the new suite of emerging genetic-engineering technologies discussed in Chapter 7 is dramatically enhancing the ability of scientists to develop potentially effective new plant traits. Future GE crops discussed in Chapter 8 could greatly expand the use of agricultural biotechnology in the development of biofuels, forestry restoration, and industrial bioprocessing and thus potentially lead to new risk-assessment and risk-management issues (NRC, 2015). This policy option thus would have the effect of shifting risk to the public; mitigation measures could be expensive and ineffective, depending on the nature of the post-market problem.

This option has practical drawbacks as well. One of the major economic concerns that has been raised is the issue of coexistence and the need to keep unapproved or undesired genetic traits out of various food- and feed-supply channels. Currently, regulators impose conditions on experimental field trials in an effort to mitigate gene flow of unapproved events from experimental field trials, although adventitious events still occur (see Chapter 6 and Box 3-2 for an example of the consequences of failing to follow those conditions). Without some similar system in place, the market could experience a substantial increase in expensive adventitious events.

Similarly, a regulatory-approval system is essential for global trade to work. Few, if any, importing countries are likely to approve GE food or feed for import or GE seed for cultivation that has not been approved as safe by the relevant regulatory authorities in the exporting country.

Finally, an important effect of a regulatory system is to enable markets by creating a credible and independent process to verify that products are safe. As noted in Chapter 2, publics in many countries, including the United States, are wary about the safety of GE crops and foods. There should be concern about the effect on public opinion if GE crops and foods are brought to market without government review for safety. Without the assurance that there has been some third-party review for safety, consumers' perceptions about the safety of GE foods and crops might erode completely. Although consumer confidence should not be the only rationale for a product-approval system, it is important to recognize that it is an important social and economic factor (OSTP, 2015).

FINDING: Not having government regulation of GE crops would be problematic for safety, trade, and other reasons and would erode public trust.

RECOMMENDATION: In determining whether a new plant variety should be subject to a premarket government approval for health and environmental safety, regulators should focus on the extent to which the characteristics of the plant variety (both intended and unintended) are likely to pose a risk to health or the environment on the basis of the novelty of traits, 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.

CONCLUSIONS

Current international agreements and national regulatory systems reflect a variety of political and regulatory approaches to GE crops and foods. All the regulatory systems examined in this report use similar risk-assessment methods to analyze the food-safety and environmental risks posed by GE crops and foods on the basis of a comparison with similar existing foods and crops. However, regulatory systems differ in approaches and policy decisions related to risk management and the level of "acceptable" risk. Thus, some countries have adopted more precautionary approaches and included socioeconomic considerations in product approvals, such as the coexistence of GE and non-GE cropping systems and consumer right-to-know.

Although such nonsafety issues are not typically considered by U.S. regulatory agencies, they are nevertheless important technology-governance issues that can be addressed by policy-makers, the private sector, and the public through a variety of governmental and nongovernmental means that take into account competing interests of stakeholders and inherent tradeoffs involved in any decision.

Accuracy and trust are critical for technology governance. The committee renews the advice from prior National Research Council reports to regulatory agencies to expand efforts to include the public in their deliberations and to make their decisions and the information on which they base their decisions as transparent as possible, recognizing the constraints of various laws that protect confidential business information and other sensitive data. Similarly, the committee emphasizes that governance authorities should actively seek public input on decisions, including decisions regarding how to approach emerging genetic-engineering technologies (such as genome editing and synthetic biology) and their regulation.

The power to require continued monitoring or controls after a crop has been approved is a critical tool for regulators, particularly when there are known risks or there is some residual uncertainty at the time of approval. The development of herbicide resistance in weeds might have been mitigated if APHIS had had the authority to make mid-course corrections after there was experience on a commercial scale.

Prior National Research Council reports have argued that there is no strict dichotomy between genetic engineering and other forms of plant breeding with respect to risk. Recent developments in genome editing and other emerging genetic-engineering technologies make it even more apparent that regulatory approaches that focus on some form of breeding "process" as an indicator of risk are less and less technically defensible. Some emerging genetic-engineering technologies are likely to create new crop varieties that are indistinguishable from those developed with conventional plant breeding, whereas other technologies, such as mutagenesis, that are not covered by existing laws could create new crop varieties with substantial changes to plant phenotypes. The size and extent of the genetic transformation has relatively little relevance to the extent of the change in the plant and consequently to the risk that it poses to the environment or to food safety. The committee recommends the development of a tiered approach to regulation that is based not on the breeding process but on considerations of novelty, potential hazard, and exposure as criteria. The application of -omics technologies can help to provide greater assurance that no unintended differences have been introduced by whatever breeding technique is used.

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Appendix A

Biographical Sketches of Committee Members

Fred Gould (Chair) is a University Distinguished Professor of Entomology and codirector of the Genetic Engineering and Society Center at North Carolina State University. He studies the ecology and genetics of insect pests to improve food production and human and environmental health. Dr. Gould's research on the application of evolutionary biology and ecological genetics to sustainable insect-pest management has influenced management of insect pests of crops on a global scale and promises to do the same for arthropod vectors of human disease. He has been a leader in shaping the science-based regulatory framework for the deployment of *Bt* crops in the United States and globally. His research and major contributions have earned him numerous national and international awards, including the Alexander von Humboldt Award in 2004, which is presented annually to the person judged to have made the most important contribution to American agriculture during the previous 5 years. In 2011, he was elected to the U.S. National Academy of Sciences (NAS). Dr. Gould has served on several NAS–National Research Council committees studying effects of the commercialization of genetically engineered crops. He currently serves on the National Academies of Sciences, Engineering, and Medicine's Board on Agriculture and Natural Resources. He is a fellow of the Entomological Society of America and of the American Association for the Advancement of Science. Dr. Gould is the author or a coauthor of more than 180 refereed publications. He received his BS in biology from Queens College and a PhD in ecology and evolutionary biology from the State University of New York at Stony Brook.

Richard M. Amasino is a professor in the Department of Biochemistry of the University of Wisconsin–Madison. His work focuses on how plants perceive seasonal cues, such as changing day length and temperature, and how they use such cues to determine when to initiate flowering. His most recent focus has been on understanding the biochemical pathway through which perception of winter cold leads to flowering in the spring—a process known as vernalization. Dr. Amasino is also a member of the Great Lakes Bioenergy Research Center, which is one of the three bioenergy research centers established by the U.S. Department of Energy. His work with the center involves studying the biochemical basis of plant biomass accumulation and directing the education and outreach program of the center. Dr. Amasino is a Howard Hughes Medical Institute professor, a member of the U.S. National Academy of Sciences, and a fellow of the American Association for the Advancement of Science. His teaching and research have resulted in several national and international awards, including the Alexander von Humboldt Foundation Award in 1999. He has served as president and chair of the board of trustees of the American Society of Plant Biologists. Dr. Amasino received his BS in biology from Pennsylvania State University and his MS and PhD in biology and biochemistry from Indiana University.

Dominique Brossard is a professor in and chair of the Department of Life Sciences Communication at the University of Wisconsin–Madison (UW–Madison). She is an affiliate of the UW–Madison Robert and Jean Holtz Center for Science and Technology Studies, the UW–Madison Center for Global Studies, and the Morgridge Institute for Research. Dr. Brossard teaches courses in strategic communication theory and research with a focus on science and risk communication. Her research program concentrates on the intersections between science, media, and policy. A fellow of the American Association for the Advancement of Science and a former member of the board of the International Network of Public Communication of Science and Technology, Dr. Brossard is an internationally known expert in public-opinion dynamics related to controversial scientific issues, such as genetic engineering of crops. She has published numerous research articles on the topic in such outlets as *Science*, *Science Communication*, the *Proceedings of the National Academy of Sciences of the United States of America*, the *International Journal of Public Opinion Research*, *Public Understanding of Science*, and *Communication Research* and was coeditor of the 2007 book *The Media, the Public, and Agricultural Biotechnology*. Dr. Brossard has a varied professional background, including experience in the laboratory and in the corporate world. She spent 5 years at Accenture in its Change Management Services Division. She was also the communication coordinator for the Agricultural Biotechnology Support Project II (ABSPII), a position that combined public relations with marketing communication and strategic communication. Dr. Brossard earned her MS in plant biotechnology from the Ecole Nationale d'Agronomie de Toulouse and her MPS and PhD in communication from Cornell University.

C. Robin Buell joined the Department of Plant Biology of Michigan State University in October 2007 after spending 9 years at The Institute for Genomic Research. She studies plant genome biology and deciphers the genomes of plant pathogens. Her research also uncovers how components of the genome confer function and phenotype on a plant and on microorganisms that feed on it. Dr. Buell has published extensively on plant genomics and bioinformatics. She has worked on the genomes of *Arabidopsis*, rice, potato, maize, switchgrass, and medicinal plants. Dr. Buell earned her BS from the University of Maryland, her MS from Washington State University, and her PhD from Utah State University. She has an active research group composed of postdoctoral research fellows, research assistants, graduate students, undergraduate students, and high school interns and collaborates with scientists across the United States and throughout the world. Dr. Buell has served as an editor at *Plant Physiology*, *The Plant Genome*, *Crop Science*, *Frontiers in Plant Genetics and Genomics*, and *The Plant Cell*. She is a fellow of the American Association for the Advancement of Science and the American Society of Plant Biologists, a Michigan State University Foundation Professor, and a recipient of the Michigan State University William J. Beal Distinguished Faculty Award.

Richard A. Dixon is director of the BioDiscovery Institute and Distinguished Research Professor in the Department of Biological Sciences of the University of North Texas. He was previously Distinguished Professor and Samuel Roberts Noble Research Chair, senior vice president, and founding director of the Plant Biology Division of the Samuel Roberts Noble Foundation in Ardmore, Oklahoma, where he worked from 1988 to 2013. Dr. Dixon's research centers on the biochemistry, molecular biology, and metabolic engineering of plant natural-product pathways and their implications for agriculture and human health. He is also interested in engineering of lignocellulosic biomass for the improvement of forage and bioenergy feedstocks. He has published over 450 papers and chapters on those and related topics in international journals. He is a member of the editorial boards of five international journals and has been named by the Institute for Scientific Information as one of the 10 most-cited authors in the plant and animal sciences. Dr. Dixon is a member of the U.S. National Academy of Sciences and a fellow of the National Academy of Inventors and of the American Association for the Advancement of Science. He received his BS and PhD in biochemistry and botany from the University of Oxford, UK, and postdoctoral training in plant biochemistry at the University of

Cambridge. He was awarded a DSc for his research achievements by the University of Oxford in 2004.

José B. Falck-Zepeda joined the International Food Policy Research Institute (IFPRI) in 2004 as a research fellow. He is now a senior research fellow and leader of the Policy Research Team of the Program for Biosafety Systems. His work at IFPRI focuses on the economics and impact assessment of agricultural biotechnology, biosafety, and other emerging technologies. Dr. Falck-Zepeda also conducts research on agricultural R&D and science policy, investments, and technical innovation capacity in developing countries. His research has examined such diverse topics as the socioeconomic impact of *Bt* and Roundup Ready cotton and maize and other genetically modified plants, the cost of compliance with biosafety regulations and their impact on investment flows, biotechnology capacity in Latin America and Africa, and the determinants of technology adoption in developing and developed countries. Before joining IFPRI, Dr. Falck-Zepeda worked as a research officer at the International Service for National Agricultural Research (ISNAR) in The Hague, the Netherlands. He also was a postdoctoral research fellow at Auburn University and an assistant professor and instructor at the Panamerican Agricultural School (Zamorano University) in Honduras. Dr. Falck-Zepeda is the author of multiple books, journal articles, and other publications and has been an invited speaker in high-level policy dialogues and professional conferences globally. A citizen of Honduras, he holds an agronomy degree from the Panamerican Agricultural School (Zamorano University), a BS in animal science from Texas A&M University, and an MS and a PhD in agricultural economics from Auburn University.

Michael A. Gallo is Emeritus Professor (Environmental and Occupational Medicine) at Rutgers-Robert Wood Johnson Medical School. He is also an adjunct professor in the School of Public Health and the Department of Pharmacology and Toxicology of the Ernest Mario School of Pharmacy of Rutgers. He was the founding (interim) director of the Cancer Institute of New Jersey and a founder of the Environmental and Occupational Health Sciences Institute at Rutgers. In addition he served as the Senior Associate Dean for Research of the medical school. His expertise includes dioxins and polychlorinated biphenyls (PCBs), experimental models in pharmacology and toxicology, cytoplasmic and cell-surface receptors, hormone biology, and mechanisms of hormonal and environmental carcinogenesis. Dr. Gallo has served on several National Academy of Sciences and National Research Council committees, such as the Roundtable on Environmental Health Sciences, Research, and Medicine; the Committee on Pesticides in the Diets of Infants and Children; the Committee on Risk Assessment Methodology; and the Committee on Safe Drinking Water. He was granted the Society of

Toxicology Education Award, chaired the Hormonal Carcinogenesis and the Mechanisms of Toxicity Gordon Research Conferences, and served as ambassador of toxicology of the Mid-Atlantic Society of Toxicology. Dr. Gallo received his BA in biology and chemistry from Russell Sage College and received his PhD in toxicology and experimental pathology from Albany Medical College of Union University.

Ken Giller is a professor of plant production systems in the Wageningen Centre for Agroecology and Systems Analysis of Wageningen University. He leads a group of scientists who have profound experience in applying systems analysis to explore future scenarios of land use with a focus on food production. Dr. Giller's research has focused on smallholder farming systems in sub-Saharan Africa, particularly problems of soil fertility and the role of nitrogen fixation in tropical legumes with emphasis on the temporal and spatial dynamics of resources in crop–livestock farming systems and their interactions. He is the author of the standard text, *Nitrogen Fixation in Tropical Cropping Systems*, whose second edition was published in 2001. He leads a number of initiatives, such as N2Africa (Putting Nitrogen Fixation to Work for Smallholder Farmers in Africa), NUANCES (Nutrient Use in Animal and Cropping Systems: Efficiencies and Scales), and Competing Claims on Natural Resources. Dr. Giller joined Wageningen University as chair of plant-production systems in 2001 after holding professorships at Wye College, University of London, and the University of Zimbabwe. He holds a PhD in ecology from Sheffield University.

Leland L. Glenna is an associate professor of rural sociology and science, technology, and society in the Agricultural Economics, Sociology, and Education Department of The Pennsylvania State University. His research and teaching fit into three areas of emphasis: the social and environmental impacts of agricultural science and technology, the role of science and technology in agricultural and environmental policy-making, and the social and ethical implications of democratizing science and technology research. His domestic research focuses on how research funding for and research outputs of university–industry research collaborations in agricultural and food science change over time, especially with respect to genetic-engineering technology. His current international research projects focus on agricultural and community development and on international comparative analyses of agricultural research funding and innovations. Prior to his time at Penn State, he served as a postdoctoral associate and lecturer at Cornell University, a research sociologist at the University of California, Davis, and an assistant professor at Washington State University. Dr. Glenna received his bachelor's degree in history from Hamline University, his master's of divinity from Harvard Divinity School, and his PhD in rural sociology from the University of Missouri.

Timothy S. Griffin is an associate professor in the Friedman School of Nutrition Science and Policy of Tufts University. He directs the interdisciplinary graduate program Agriculture, Food and the Environment and teaches classes on U.S. agriculture, agricultural science and policy, and the intersection of ecology and technology. He also serves on the steering committee for the university-wide graduate program Water: Systems, Science and Society and is a faculty codirector of the Tufts Institute for the Environment and a faculty affiliate at the Center for International Environment and Resource Policy at Tufts. His research focuses on barriers to and incentives for regional food systems, environmental effects of agriculture, climate change, and conservation practices in agricultural systems. Before coming to the Friedman School in 2008, Dr. Griffin was research agronomist and lead scientist with the U.S. Department of Agriculture Agricultural Research Service in Orono, Maine, from 2000 to 2008. He conducted research on many aspects of agricultural production in the northeastern United States, including nutrient cycling and grain production on organic dairy farms, crop management, and long-term sustainability of high-value production systems. He also initiated research on greenhouse-gas emissions, soil carbon and nitrogen cycling, and soil conservation in those systems. From 1992 to 2000, Dr. Griffin was an extension sustainable-agriculture specialist at the University of Maine, the first such position in the United States. He developed and delivered a wide-ranging educational and applied-research program on crop production, nutrient availability, and crop–livestock integration. He received his BS in forage and range management and his MS in agronomy from the University of Nebraska and his PhD in crop and soil science from Michigan State University.

Bruce R. Hamaker is Distinguished Professor of Food Science, director of the Whistler Center of Carbohydrate Research, and holder of the Roy L. Whistler Chair in Carbohydrate Science in the Department of Food Science of Purdue University, West Lafayette, Indiana. He obtained his undergraduate degree in biological sciences from Indiana University; his graduate studies, at Purdue, were in human nutrition (MS) and food chemistry (PhD); and he did postdoctoral study at the Instituto de Investigacion Nutricional in Lima, Peru. He was in the U.S. Peace Corps in Liberia from 1977 to 1979. Dr. Hamaker has over 170 refereed journal publications in food science, human nutrition, biochemistry, and broad-spectrum journals and numerous book chapters. He has advised over 50 MS and PhD students and nearly 20 postdoctoral scientists. Dr. Hamaker's research program is known for its focus on food carbohydrates and proteins with applications related to health and wellness. In that regard, he has a number of clinical and nutrition-science collaborations and research experience in protein and carbohydrate digestion patterns related to quality and physiological response and in dietary-fiber effect on the gut microbiome. Dr. Hamaker works with ingredient and processed-food companies principally to assist in improving nutritional or health quality of processed products. He is active in international research collaborations in Africa and Asia. In Africa, he has worked for over 20 years on publicly funded and foundation-funded projects on improvement of utilization and nutritional properties of cereal grains and on setting up technology-based incubation centers to work with local entrepreneurs.

Peter M. Kareiva is the director of the Institute of the Environment and Sustainability at the University of California, Los Angeles, and the chair of the Science Cabinet at The Nature Conservancy. He is cofounder (with Gretchen Daily and Taylor Ricketts) of the Natural Capital Project, a pioneering partnership among The Nature Conservancy, Stanford University, and WWF. The Natural Capital Project develops models that quantify nature's assets (or ecosystem services) with the aim of informing the choices that people make on the scale of local communities and regions up to nations and global agreements. Dr. Kareiva is the author of more than 150 scientific publications in such journals as *Nature*, *Science*, and the *Proceedings of the National Academy of Sciences of the United States of America*. He has published on gene-flow issues and environmental risk analysis related to genetically engineered crops. He was named a member of the National Academy of Sciences in 2011. He is also a fellow of the American Academy of Arts and Sciences and a member of the Ecological Society of America and the Society for Conservation Biology. Dr. Kareiva received his BA in zoology from Duke University, his MS in environmental biology from the University of California, Irvine, and his PhD in ecology and evolutionary biology from Cornell University.

Daniel Magraw is Professorial Lecturer and Senior Fellow of the Foreign Policy Institute of Johns Hopkins University's School of Advanced International Studies (SAIS). He has extensive experience in international law, institutions, processes and policies, particularly in relation to environmental protection, dispute settlement, and human rights. He has worked in government, nongovernmental organizations, intergovernmental organizations, business, and academe. Mr. Magraw was a member of the National Research Council Committee on the Biological Confinement of Genetically Engineered Organisms and a member of the U.S. government's Trade and Environment Policy Advisory Committee. While in the U.S. government during 1992–2001, he cochaired a White House assessment of the regulation of genetically engineered organisms and was director of the International Environmental Law Office and acting principal deputy assistant administrator in the Office of International Activities of the U.S. Environmental Protection Agency. He has taught at the University of California, Berkeley, the University of Colorado, the University of Miami, and the Georgetown University Law Center. He worked as an economist and business consultant in India as a Peace Corps volunteer. Mr. Magraw has a JD from the University of California, Berkeley, where he was editor-in-chief of the *California Law Review*, and a BA (magna cum laude) in economics from Harvard University.

Carol Mallory-Smith is a professor of weed science in the Department of Crop and Soil Science of Oregon State University. She earned her BS in plant protection and her PhD in plant science from the University of Idaho. Her main research interests are gene flow and hybridization between crops and weeds (including genetically engineered and conventionally bred), herbicide resistance, weed management in agronomic crops, and weed biology. She is the author or coauthor of more than 120 journal articles, eight book chapters, and numerous extension and popular-press articles. Dr. Mallory-Smith visited Australia and Korea as an invited expert on gene flow and other weed issues. She has been an invited speaker in Australia, France, Korea, and Thailand to address the potential risks and benefits of introducing genetically engineered crops. Dr. Mallory-Smith served as a Fulbright Scholar lecturer in Argentina. She is a fellow of the Western Society of Weed Science (WSWS) and the Weed Science Society of America (WSSA) and served as president and treasurer of WSSA and secretary–treasurer of the International Weed Science Society. Dr. Mallory-Smith's awards include the Alumni Achievement Award from the University of Idaho's College of Agriculture in 2007, the Excellence in Graduate Mentoring Award from Oregon State University in 2009, the WSWS Outstanding Weed Scientist in 2009, the Distinguished Service Award for Individual Contribution to the Agricultural Industry by the Oregon Department of Agriculture in 2014, and the WSSA Outstanding Researcher Award in 2016.

Kevin Pixley is the director of the Genetic Resources Program of the International Maize and Wheat Improvement Center (CIMMYT), a position he has held since 2011. He joined CIMMYT as a postdoctoral fellow in 1990 and served as a maize breeder (1993) and then also as team leader (1997) at the center's Harare, Zimbabwe, research station. After 11 years in Africa, he returned to CIMMYT headquarters in Mexico to serve in directing positions in the Global Maize Program with primary responsibilities in Asia and Latin America while leading CIMMYT's breeding program and a multidisciplinary global network of scientists developing nutritionally enhanced maize. His responsibilities include oversight of research to characterize and facilitate use of genetic resources and biosafety related to transgenic maize and wheat research at CIMMYT. Dr. Pixley is also an adjunct associate professor at the University of Wisconsin, where he teaches about agriculture, health, and nutrition and their roles in household livelihoods and international development. His accomplishments include mentoring 12 undergraduate and 12 graduate students in their thesis projects, being the author of more than 50 refereed journal articles and book chapters, and leading international collaborative maize-breeding projects for enhanced disease resistance and nutritional quality. Dr. Pixley received his BS from Purdue University, his MS in crop physiology from the University of Florida, and his PhD in plant breeding from Iowa State University.

Elizabeth P. Ransom is an associate professor of sociology in the Department of Sociology and Anthropology of the University of Richmond. Her research focuses on international development and globalization, the sociology of agriculture and food, and social studies of science and technology. Specifically, she concentrates on the intersection of science and technology policy within agriculture and food systems with emphasis on how policy changes affect producers and production practices in the United States and sub-Saharan Africa. Her previous research focused on agricultural biotechnologies and cross-national pesticide regulations. She has two ongoing research programs. The first studies the linkages between southern Africa (South Africa, Botswana, and Namibia) red-meat industries and global agriculture and food systems governance. The second analyzes international agricultural development assistance in developing countries with an emphasis on how agricultural assistance targets women and focuses on gender empowerment. She has published articles on agricultural biotechnologies, the patterns and problems surrounding modern food-consumption practices, the global red-meat trade, and gender and agricultural development assistance. As a 2005-2006 American Association for the Advancement of Science policy fellow, Dr. Ransom focused on Codex Alimentarius agrifood standards as an international trade specialist at the U.S. Department of Agriculture. In addition to her position at the University of Richmond, she is a research associate with the Institute of Theory and Practice of International Relations at the College of William and Mary. Dr. Ransom received her BA in sociology and political science from Western Carolina University and her MA and PhD in sociology from Michigan State University.

Michael Rodemeyer completed his adjunct professorship in 2015 in the Department of Engineering and Society of the University of Virginia, where he taught and directed the Science and Technology Policy Internship Program. Mr. Rodemeyer founded the Pew Initiative on Food and Biotechnology and served as its executive director from 2000 to 2005. Before that, he spent nearly 25 years in the federal government. In 1998 and 1999, he was the assistant director for environment in the Office of Science and Technology Policy in the Executive Office of the President. He served for 15 years on the staff of the House of Representatives Committee on Science, including 7 years as the Chief Democratic Counsel. From 1976 through 1984, Mr. Rodemeyer was a staff attorney with the Federal Trade Commission. He also taught congressional and environmental policy-making as an adjunct professor of the Johns Hopkins University School of Arts and Sciences from 2000 through 2004. Mr. Rodemeyer graduated with honors from Harvard Law School in 1975 and received his undergraduate degree in sociology with honors from Princeton University in 1972.

David M. Stelly holds joint appointments with Texas A&M University and Texas A&M AgriLife Research. He is a professor in the Department of Soil and Crop Sciences and has over 30 years of professional experience in breeding of diploid and polyploid crops, germplasm introgression, reproductive biology and cytology, cytogenetics, genetics, and genomics. The research, breeding, and graduate-education programs under Dr. Stelly's guidance have emphasized use of naturally occurring germplasm for crop improvement. Common elements of the research are wild-species germplasm introgression, chromosome manipulations and substitution, ploidy manipulations, conventional and molecular cytogenetics, genetic analysis, marker development, marker-assisted selection, reproductive cytology and genetics, and various types of genome mapping (linkage, BAC physical, and radiation hybrid mapping), sequencing, and their integration. Most of his work has been devoted to genetic improvement of Upland cotton, but some of it is devoted to developing a platform for wide hybridization of sorghum and creation of new energy crops. Dr. Stelly has served Texas A&M through its Council for Principal Investigators, where he helped spawn and now serves on the Texas A&M Institute for Genome Sciences and Society. He also codirects his department's faculty-driven core AgriGenomics Laboratory. He served a number of years ago as the first elected chair of the International Cotton Genome Initiative and was recently elected to serve again. He has also been president of the National Association of Plant Breeders. Dr. Stelly received his MS in plant breeding and cytogenetics from Iowa State University and his BS in Genetics and PhD in plant breeding and plant genetics from the University of Wisconsin–Madison.

C. Neal Stewart is a professor of plant sciences at the University of Tennessee and holds the Ivan Racheff Chair of Excellence in plant molecular genetics. He is also codirector of the Tennessee Plant Research Center. After a postdoctoral position at the University of Georgia, Dr. Stewart joined the faculty of the University of North Carolina at Greensboro as an assistant professor, and then associate professor in biology before moving to the University of Tennessee and assuming the Racheff Chair. He teaches courses on plant biotechnology and research ethics. His laboratory's research spans plant biotechnology, synthetic biology, genomics, and ecology with an interest in understanding and manipulating systems relative to agricultural production and environmental function. Dr. Stewart earned his BS in horticulture and agricultural education from North Carolina State University and an MA in education from Appalachian State University. He then received an MS in biology and ecology and a PhD in biology and plant physiology from Virginia Polytechnic Institute and State University. Dr. Stewart is also a singer and songwriter.

Robert Whitaker received his PhD in biology from the State University of New York at Binghamton in 1982. On graduating, he joined DNA Plant Technology Corporation as a postdoctoral research scientist and eventually served as both vice president for vegetable research and development and vice president for product development for the company. During his tenure there, Dr. Whitaker had responsibility for plant tissue culture, breeding, food science, chemistry, and genetic-engineering functions related to vegetable products. In 1998, he joined NewStar as vice president of product development and quality; there, he developed corporate food-safety programs and spearheaded product-development activities. In April 2008, he became the chief science and technology officer of the Produce Marketing Association, overseeing food-safety and technology efforts from field to fork. He has served as a volunteer leader for the United Fresh Produce Association and as chairman of the board of the International Fresh-cut Produce Association (IFPA) and has been directly involved in a number of industry and government food-safety and technology initiatives. In 2006, Dr. Whitaker was awarded IFPA's Technical Achievement Award for his work in food safety and product development. He also received the NSF Food Safety Leadership award in 2015. Dr. Whitaker was named to the Executive Committee of the Center for Produce Safety (CPS) in 2007 and served as chairman of the CPS Technical Committee until 2013. He still serves as a member of the CPS Technical Committee, which oversees the solicitation and awarding of funds for produce food-safety research, and on the Executive Committee of the CPS Board of Directors.

Appendix B

Revisions to the Statement of Task

Building on and updating the concepts and questions raised in previous NRC 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 ~~basis of~~ 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 ~~basis of~~ 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 innovation in and access to GE technology.

The committee will produce a report directed at policy-makers ~~as well as~~ that will serve as the basis for derivative products designed for a lay audience.

Revised 11/18/2014

Appendix C

Agendas of Information-Gathering Sessions

Information-gathering sessions include in-person public meetings and webinars held by the committee from September 2014 to May 2015. They are listed in chronological order. The locations of in-person meetings are provided. Presentations that were made via the Internet at the in-person public meetings are noted.

September 15-16, 2014

The first in-person public meeting of the Committee on Genetically Engineered Crops: Past Experience and Future Prospects was held at the National Academy of Sciences building in Washington, DC.

Agenda
Monday, September 15, 2014
1PM-6:15PM

1:00 **Welcome**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

Committee Introductions

1:20 ***Major Goodman***, Member of the National Academy of Sciences and William Neal Reynolds and Distinguished University Professor of Crop Science, Statistics, Genetics, and Botany

1:40 ***R. James Cook***, Member of the National Academy of Sciences and Professor Emeritus, Washington State University

2:00 ***Ian Baldwin***, Member of the National Academy of Sciences and Professor, Max Planck Institute for Chemical Ecology

2:20 **Committee Discussion with Presenters**

2:40 *Break*

3:00 ***Chuck Benbrook***, Research Professor, Center for Sustainable Agriculture and Natural Resources, Washington State University

3:20 ***Glenn Stone***, Professor of Anthropology and Environmental Studies, Washington University in St. Louis

3:40 ***Hope Shand***, Independent Consultant and Senior Advisor, Erosion, Technology and Concentration (ETC) Group

4:00 **Committee Discussion with Presenters**

4:45 *Break*

5:00 **Introduction to the Public Comment Session**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

5:15 **Public Comment**

6:15 **Public Meeting Adjourns**

Tuesday, September 16, 2014
9AM-6:15PM

9:00 **Welcome**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

Committee Introductions

9:30 ***Dietram Scheufele***, Co-chair, National Research Council Roundtable on Public Interfaces of the Life Sciences and John E. Ross Professor in Science Communication, University of Wisconsin, Madison

9:50 ***Jennifer Kuzma***, Goodnight-Glaxo Wellcome Distinguished Professor and Codirector of the Genetic Engineering and Society Center, North Carolina State University

10:10 ***Carmen Bain***, Associate Professor of Sociology, Iowa State University

10:30 *Break*

10:50 ***Gilles-Éric Séralini***,[1] Professor of Molecular Biology, University of Caen, France, and Director of the Network on Risks, Quality, and Sustainable Environment

11:10 ***Jeffrey Smith***,[2] Founding Executive Director, Institute for Responsible Technology

11:30 ***Janet Cotter***,[3] Senior Scientist, Greenpeace International

11:50 **Committee Discussion with Presenters**

12:30 *Break*

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[1] The speaker gave his presentation via the Internet.
[2] The speaker gave his presentation via the Internet.
[3] The speaker gave her presentation via the Internet.

1:30 ***Greg Jaffe***, Director of the Project on Biotechnology, Center for Science in the Public Interest

1:50 ***Jon Entine***, Executive Director, Genetic Literacy Project, and Senior Fellow, World Food Center Institute for Food and Agricultural Literacy, University of California-Davis

2:10 ***Doug Gurian-Sherman***, Director of Sustainable Agriculture and Senior Scientist, Center for Food Safety
Bill Freese, Science Policy Analyst, Center for Food Safety

2:30 ***Tamar Haspel***, Journalist, The Washington Post

2:50 *Break*

3:10 ***Tim Schwab***, Senior Researcher, Food & Water Watch

3:30 ***Michael Hansen***, Senior Staff Scientist, Consumers Union

3:50 ***Lisa Griffith***, Outreach Director, National Family Farm Coalition

4:10 **Committee Discussion with Presenters**

4:45 *Break*

5:00 **Introduction to the Public Comment Session**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

5:15 **Public Comment**

6:15 **Public Meeting Adjourns**

October 1, 2014

Webinar on Perspectives on Genetically Engineered (GE) Crops from U.S. Agricultural Extension Specialists
Speakers:

Dominic Reisig, Associate Professor and Extension Specialist, North Carolina Cooperative Extension
Mohamed Khan, Professor and Extension Specialist, North Dakota State University and University of Minnesota
Rick Kersbergen, Extension Professor, University of Maine Cooperative Extension
Ben Beale, Extension Educator–Agricultural Sciences, University of Maryland Extension

October 8, 2014

Webinar on International Trade and GE Crops
Speakers:

Lee Ann Jackson, Counsellor, World Trade Organization
Randal Giroux, Vice President–Food Safety, Quality and Regulatory, Cargill, Incorporated
Lynn Clarkson, President, Clarkson Grain

October 22, 2014

Webinar on Perspectives on GE Crops from U.S. Agricultural Extension Specialists
Speakers:

Russel Higgins, Extension Educator, North Illinois Agronomy Research Center, University of Illinois Extension
Jeff Lannom, Weakley County, Extension Director, University of Tennessee Extension
Diana Roberts, Regional Extension Specialist, Washington State University Extension
Dallas Peterson, Professor and Extension Weed Specialist, Kansas State University

November 6, 2014

Webinar on Genetically Engineered Disease Resistance in Crops
Speakers:

Richard Sayre, Senior Research Scientist, Los Alamos National Laboratory and the New Mexico Consortium
Anton Haverkort, Researcher, Wageningen University and Research Center
Ralph Scorza, Research Horticulturist, U.S. Department of Agriculture (USDA) Appalachian Fruit Research Station
Dennis Gonsalves, Director (retired), USDA Pacific Basin Agricultural Research Center

December 10, 2014

The second in-person public meeting of the Committee on Genetically Engineered Crops: Past Experience and Future Prospects was held at the National Academy of Sciences building in Washington, DC.

Agenda
Wednesday, December 10, 2014
10:30AM-6:00PM

10:30 **Welcome**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

Committee Introductions

10:45 **Study Sponsors**
Michael Schechtman, Biotechnology Coordinator, Office of Pest Management Policy, U.S. Department of Agriculture–Agricultural Research Service
Statement from the Gordon and Betty Moore Foundation

11:00 **Emerging Technologies and Synthetic Biology Approaches to GE Crops**
Dan Voytas, Professor of Genetics, Cell Biology and Development and Director, University of Minnesota Center for Genome Engineering
Andreas Weber, Head of the Institute of Plant Biochemistry, University of Düsseldorf

11:40 **Committee Discussion with Presenters**

12:00 *Break*

1:00 **Representatives from U.S. Regulatory Agencies**
John Turner, Director, Environmental Risk Analysis Programs, Biotechnology Regulatory Services, U.S. Department of Agriculture–Animal and Plant Health Inspection Service
William L. Jordan, Deputy Director for Programs, U.S. Environmental Protection Agency–Office of Pesticide Programs
Chris A. Wozniak, Biotechnology Special Assistant, U.S. Environmental Protection Agency–Office of Pesticide Programs
Jason Dietz, Policy Analyst, Office of Food Additive Safety, Food and Drug Administration–Center for Food Safety and Applied Nutrition

2:05 **Committee Discussion with Presenters**

2:45 *Break*

3:00 **Representatives from Companies Producing GE Crops**

Product Development
Sandy Endicott, Senior Agronomy Manager, DuPont Pioneer

Ray Shillito, Research and Development Fellow, Bayer CropScience

Impact on Production Agriculture
Robb Fraley, Monsanto

New Technologies
Steve Webb, External Technology and Intellectual Property Portfolio Development Leader, Dow AgroSciences

4:15 **Committee Discussion with Presenters**

4:45 *Break*

5:00 **Introduction to the Public Comment Session**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

5:15 **Public Comment**

6:00 **Public Meeting Adjourns**

January 27, 2015

Webinar on Plant Breeding at Public Institutions
Speakers:
Jim Holland, Professor, North Carolina State University
Jane Dever, Professor, Texas A&M AgriLife Research
Irwin Goldman, Professor, University of Wisconsin–Madison

February 4, 2015

Webinar on Social Science Research on GE Crop Adoption and Acceptance
Speakers:
Mary Hendrickson, Assistant Professor, University of Missouri
Matthew Schnurr, Associate Professor, Dalhousie University
Abby Kinchy, Associate Professor, Rensselaer Polytechnic Institute

February 26, 2015

Webinar Revisiting the 2004 National Research Council Report, *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects*
Speakers:
Lynn Goldman, Professor, George Washington University
Bettie Sue Masters, Distinguished Professor, University of Texas Health Science Center at San Antonio

March 5, 2015

The third in-person public meeting of the Committee on Genetically Engineered Crops: Past Experience and Future Prospects was held at the Keck Center in Washington, DC.

Agenda

Thursday, March 5, 2015
12:30PM-6:15PM

12:30 **Welcome**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

Study Process of the National Research Council
Kara Laney, Study Director, National Research Council

Committee Introductions

12:45 **Panel on Food Safety: Regulatory Perspectives**
Jason Dietz, Policy Analyst, Office of Food Additive Safety, Food and Drug Administration–Center for Food Safety and Applied Nutrition
William L. Jordan, Deputy Director for Programs, U.S. Environmental Protection Agency–Office of Pesticide Programs
John Kough, Senior Scientist, U.S. Environmental Protection Agency–Office of Pesticide Programs
Anna Lanzoni,[4] Senior Scientific Officer, European Food Safety Authority GMO Unit

2:25 **Committee Discussion with Presenters**

3:00 *Break*

3:15 **Panel on Food Safety: Potential Health Outcomes**

Evaluating GE food sources for risks of allergy: Methods, gaps, and perspectives
Richard Goodman, Research Professor, Food Allergy Research and Resource Program, University of Nebraska–Lincoln

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[4] The speaker gave her presentation via the Internet.

Potential perturbances of gastrointestinal tract mucosa of GE foods
Alessio Fasano, Vice Chair of Basic, Clinical and Translational Research and Chief of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children

Metabolomic analysis to confirm effects of transgenesis in plants
Timothy Tschaplinski, Distinguished Research Scientist and Group Leader, Metabolomics and Bioconversion, Oak Ridge National Laboratory

4:45 **Committee Discussion with Presenters**

5:15 *Break*

5:30 **Introduction to the Public Comment Session**
Fred Gould, Committee Chair, University Distinguished Professor of Entomology and Codirector of the Genetic Engineering and Society Center, North Carolina State University

5:45 **Public Comment**

6:15 **Public Meeting Adjourns**

March 19, 2015

Webinar on Socioeconomic Issues in Industrialized Countries Related to Genetically Engineered Crops
Speakers:
Keith Fuglie, Research Economist, USDA Economic Research Service
Lorraine Mitchell, Agricultural Economist, USDA Economic Research Service
Seth Wechsler, Agricultural Economist, USDA Economic Research Service
Peter Phillips, Distinguished Professor, University of Saskatchewan

March 27, 2015

Webinar on Genetically Engineered Trees
Speakers:
Steve Strauss, Professor, Oregon State University
Les Pearson, Director of Regulatory Affairs, ArborGen

Bill Powell, Professor, State University of New York's College of Environmental Science and Forestry

April 6, 2015

Webinar on GE Crops and the Microbiome
Speaker:

Jonathan Eisen, Professor, University of California–Davis

April 21, 2015

Webinar on Genetically Engineered Quality Traits
Speakers:

Neal Carter, President, Okanagan Specialty Fruits
Mark McCaslin, Vice President–Research, Forage Genetics International
Craig Richael, Director of Research and Development, Simplot Plant Sciences

April 30, 2015

Webinar on GE Agriculture and Donor Organizations
Speakers:

Rob Horsch, Deputy Director, Global Development, The Bill & Melinda Gates Foundation
John McMurdy, International Research and Biotechnology Advisor, Bureau of Food Security, U.S. Agency for International Development
Brian Dowd-Uribe, Assistant Professor, UN-mandated University for Peace

May 6, 2015

Webinar on Intellectual Property Issues of Genetically Engineered Crops
Speakers:

Alan Bennett, Executive Director, Public Intellectual Property Resources for Agriculture, and Distinguished Professor, University of California–Davis
Diana Horvath, President, Two Blades Foundation
Richard Jefferson, Founder and CEO, Cambia, and Professor of Science, Technology and Law, Queensland University of Technology

May 7, 2015

Webinar on RNA Interference Technology
Speakers:

- ***Stephen Chan***, Assistant Professor of Medicine, Harvard Medical School
- ***David Heckel***, Professor, Max Planck Institute for Chemical Ecology

May 13, 2015

Webinar on Socioeconomic Issues in Developing Countries Related to Genetically Engineered Crops
Speakers:

- ***Samuel Timpo***, Associate Director, African Biosafety Network of Expertise, New Partnership for Africa's Development
- ***Matin Qaim***, Professor of International Food Economics and Rural Development, University of Göttingen
- ***Justus Wesseler***, Professor of Agricultural Economics and Rural Policy, Wageningen University

Appendix D

Agenda for Workshop on Comparing the Environmental Effects of Pest Management Practices Across Cropping Systems

Wednesday, March 4, 2015
Keck Center
500 Fifth Street NW
Washington, DC

8:15 am–8:30 am **Welcome**

Norman Scott, Chairman, National Research Council Board on Agriculture and Natural Resources, Workshop Moderator

8:30 am–9:15 am **Keynote: Examining the Environmental Effects of Practices for Controlling Agricultural Pests**

May Berenbaum,[1] University of Illinois Urbana-Champaign, Professor and Department Chair of Entomology
Topic: Broad discussion of environmental issues surrounding agricultural production systems. Topics include pesticide residues; biodiversity; emergence of weed resistance and consequences for the environment and production; soil health; soil and nutrient losses; water quality and quantity; energy use; air quality; tradeoffs in yield; scale effects.

9:15 am–9:30 am Discussion

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[1] The speaker gave her presentation via the Internet.

9:30 am–9:45 am *Break*

9:45 am–11:05 am **Panel I: Contemporary Practices for Suppressing Weeds**

Jay Hill, New Mexico Farmer
Topic: Pest management in corn and vegetable production

Steven Mirsky, USDA–ARS, Research Ecologist
Topic: Ecologically-based weed management in long-term cropping studies

David Mortensen, Pennsylvania State University, Professor of Weed and Applied Plant Ecology
Topic: Sustainable weed management in herbicide-resistant cropping systems

Jennifer Schmidt, Maryland Farmer and Registered Dietitian
Topic: Integrating weed, pest, and disease management across crops within farming

11:05 am–12:00 pm **Discussion of Environmental Effects, Tradeoffs, and Synergies**

12:00 pm–1:00 pm *Lunch Break*

1:00 pm–2:20 pm **Panel II: Insect Management Across Production Systems**

Galen Dively, University of Maryland, Professor Emeritus, and IPM Consultant
Topic: Regional suppression of the European corn borer and its impacts on other host crops due to the *Bt* corn technology

Jonathan Lundgren, USDA–ARS, Research Entomologist
Topic: Managing insect communities in the agroecosystem

John Tooker, Pennsylvania State University, Associate Professor of Entomology, Extension Specialist
Topic: Complex ecological effects of pest-management approaches

Frank Shotkoski, Cornell University, Director of the Agriculture Biotechnology Support Project II
Topic: Examination of *Bt* eggplant release in Bangladesh

2:20 pm–3:00 pm **Discussion of Environmental Effects, Tradeoffs, and Synergies**

3:00 pm–3:15 pm *Break*

3:15 pm–4:00 pm **Panel III: Managing Pests in Tree Crops**

Harold Browning, Chief Officer of the Citrus Research and Development Foundation, Inc.
Topic: Pest management in citrus: Past, present and future

Marc Fuchs, Cornell University, Associate Professor
Topic: Virus-resistance: Lessons and prospects

4:00 pm–4:30 pm **Discussion of Environmental Effects, Tradeoffs, and Synergies**

4:30 pm–5:15 pm **Conclusions**

Topic: Discussion summarizing information gaps and research needs across different pest-management practices and agricultural production systems

Appendix E

Invited Speakers Unavailable to Present to the Committee

This list of invited speakers includes those who were unavailable to present to the committee, who declined the committee's invitation, and who did not respond to the committee's invitation.

David Andow, Distinguished McKnight University Professor, Department of Entomology, University of Minnesota
Rachel Bezner Kerr, Associate Professor of Development Sociology, Cornell University
Mark Bittman, Writer, The New York Times
Adam Bogdanove, Professor, Plant Pathology and Plant-Microbe Biology Section, School of Integrative Plant Science, Cornell University
Edward Buckler, Research Geneticist, U.S. Department of Agriculture Agricultural Research Service
Daniel Cahoy, Professor of Business Law, Smeal College of Business, Pennsylvania State University
Amy Harmon, Journalist, The New York Times
Harry Klee, Professor, Horticultural Sciences Department and Plant Molecular and Cellular Biology Program, University of Florida
Susan McCouch, Professor, Department of Plant Breeding and Genetics, Cornell University
Craig Mello, Distinguished Professor, Blais University Chair in Molecular Medicine and Codirector RNA Therapeutics Institute, University of Massachusetts Medical School
T. Erik Mirkov, Professor of Plant Molecular Virology, Texas A&M University

Bill Moseley, Professor and Department Chair of Geography, Macalester College
William Munro, Professor of Political Science, Illinois Wesleyan University
Kurt Nolte, Yuma County Extension Director, University of Arizona
Michael Pollan, Writer and Knight Professor of Science and Environmental Journalism, University of California–Berkeley
Daphne Preuss, CEO, Chromatin Inc.
José Sarukhán, Coordinador Nacional, Comisión Nacional para el Conocimiento y Uso de la Biodiversidad
Ron Phillips, Regents' Professor and McKnight Presidential Chair in Genomics, University of Minnesota
Rachel Schurman, Professor of Sociology, University of Minnesota
Syngenta representative, Syngenta North America
Terry Torneten, Regional Extension Education Director, Iowa State University Extension
Sarah Zukoff, Assistant Professor of Entomology, Kansas State University

Appendix F

Summarized Comments Received from Members of the Public

Tables F-1, F-2, and F-3 summarize the comments received from the public regarding potential effects of genetically engineered crops as well as questions and suggestions. When multiple comments focused on the same issue, one was selected as representative. The second column of the table describes the general topic related to each comment, and the third column directs the reader to the location in the report where the relevant claim is addressed.

TABLE F-1 Public Comments Regarding Potential Adverse Effects of Genetically Engineered (GE) Crops and Their Accompanying Technologies

	General Description	Page Number(s)
Agronomic		
The net gain/increases in yields due to GE crops have been overstated.	Effects of genetic engineering on yield	98–104
Insect-resistant GE crops rely on *Bt* toxins. These additional proteins come at a cost to the plant's productivity. Because insect-resistant transgenes typically go into male parents, the 'best' *Bt* transgenes can effectively kill some inbred seedlings.	Effects of genetic engineering on yield	104–116
Soil erosion rates in U.S. agriculture declined before the introduction of HR crops and have not declined since their introduction.	Effects on soil health and runoff	152–154
The dominance of any specific hybrid or variety in one crop over a major geographical segment of the market should be of concern. The pervasive planting of GE crops modified for one or two traits presents an opportunity for a wipe out by blight.	Genetic diversity in crop varieties	143–146
Greater use of crops with resistance to more than one herbicide will lead to the increase in the severity of resistant weeds.	Effects of insect and weed resistance	136–139
Environmental		
Herbicide-resistant crops promote greater use of and dependence on toxic herbicides, harming human health and the environment.	Effects of pesticide residues	133–135
The current predominant GE crops and traits have exacerbated several of the problems associated with industrial agriculture, such as increased pesticide use and pest resistance.	Effects of insecticide and herbicide use Effects of insect and weed resistance	116–121, 122–126, 133–135, 136–139
Resistance to *Bt* is rapidly emerging and spreading.	Effects of insecticide and herbicide use	122–126
IR traits have not deterred the rise in the use of neonicotinoids because the spectrum of insects susceptible to *Bt* toxins is narrow. Neonicotinoids are highly toxic to many vertebrates and persistent in the environment.	Effects of insecticide and herbicide use	120,142

TABLE F-1 Continued

	General Description	Page Number(s)
Herbicide use associated with GE crops has caused herbicide-resistant weeds. The rapid evolution of herbicide-resistant weeds creates a "transgene treadmill." It also leads to more tillage and therefore more soil erosion.	Effects of insect and weed resistance	136–139, 152–154
The planting of continuous corn because of GE has indirect and landscape-level effects like the elimination of milkweed in the Midwest and the increase in nitrate pollution and anoxic coastal zones because of the nitrate loss to leading due to the shallow root system of corn and the lack of rotation with other crops to make use of the excess nitrates.	Effects on landscape biodiversity Effects on soil health and runoff	148–150, 152–154
Herbicides like glyphosate and 2,4-D are killing honeybees.	Biodiversity within farms and fields	133–135
Glyphosate-resistant crops are negatively affecting monarch butterfly populations.	Biodiversity within farms and fields	148–150
Insect-resistant crops harm biodiversity, including natural enemies of agricultural pests.	Biodiversity within farms and fields	141–142
Bt toxins kill beneficial insects like lacewings and lady beetles. Studies that show otherwise have design flaws in which the insects do not actually ingest the toxin.	Biodiversity within farms and fields	141–142
The potential hazards posed by RNAi–based pesticides and GE crops to nontarget organisms include off-target gene silencing, silencing the target gene in unintended organisms, immune stimulation, and saturation of the RNAi machinery. The persistence of insecticidal small RNAs in the environment is unknown. It is also unknown if laboratory toxicity testing can accurately predict the field-level effects of this technology.	Biodiversity within farms and fields	416–419, 506–507
GE technology facilitates the spread of monoculture. Monoculture systems are associated with increase pest pressure, lower yields (often compensated for by higher purchased input use), leakage of nutrients causing water pollution, climate emissions, air pollution, and reduced biodiversity.	Biodiversity within farms and fields	140–154

continued

TABLE F-1 Continued

	General Description	Page Number(s)
Seed company consolidation due to GE crops has threatened biodiversity.	Biodiversity within farms and fields Genetic diversity in crop varieties	143–146
Human Health and Food Safety		
GE corn has higher levels of rotenone, a plant-produced insecticide that may cause Parkinson's disease.	Health effects of *Bt* crops	231–233
Some *Bt* proteins can enter the bloodstream intact, and some *Bt* proteins and/or fragments can survive the acidic conditions of the upper GI tract. The survival of these proteins in the GI tract could be linked to the rise in GI tract disorders in recent years.	Health effects of *Bt* crops	215–218, 221–225
Bt proteins or fragments are found in umbilical cord blood at birth.	Health effects of *Bt* crops	224–225
Bt proteins pose harm to gut walls, blood cells, fetal development, and the immune system.	Health effects of *Bt* crops	221–225
GE foods are detrimental to human health, causing sterility, cancer, asthma, autism, birth defects, chronic disease in children, and liver and kidney problems. They have caused the epidemic levels of obesity, diabetes, cancer, and allergies.	Health effects of *Bt* crops Health effects of herbicides associated with herbicide-resistant crops	207–221
There is evidence in mammal feeding studies that long-term feeding of GE corn and soybeans causes damage to kidney, liver, and bone marrow, possibly indicating chronic disease.	Health effects of *Bt* crops Health effects of herbicides associated with herbicide-resistant crops	184–198
Consumers of GE food have a higher likelihood to have multiple health issues and to consume more corn with less milling. Therefore, GE trait exposures in these populations could pose unique health-status related risks.	Health effects of *Bt* crops Health effects of herbicides associated with herbicide-resistant crops	207–225, 231–233

TABLE F-1 Continued

	General Description	Page Number(s)
Genetic engineering could lead to new animal and plant diseases, new sources of cancer, and novel epidemics.	Health effects of *Bt* crops Effects on plant disease Health effects of herbicides associated with herbicide-resistant crops	207–225, 231–233
GE crops cause gluten sensitivity by affecting intestinal permeability, imbalanced gut bacteria, immune activation and allergies, impaired digestion, and damage to the intestinal wall.	Health effects of *Bt* crops Health effects of herbicide-resistant crops	215–218, 221–225
Livestock fed GE diets require more antibiotics and have more gastrointestinal disorders and lower birth rates/litters than livestock fed non-GE diets.	Health effects of *Bt* crops Health effects of herbicide-resistant crops	195–197
GE soybean has increased levels of antinutrient soy lectin and allergen trypsin inhibitor and higher lignin content with reduced protein, a fatty acid, an essential amino acid, and phytoestrogens.	Health effects of herbicides associated with herbicide-resistant crops	193–194
Formulated pesticide mixtures have not been investigated for long-term toxicities. Long-term and multigenerational testing in vivo is needed.	Health effects of herbicides associated with herbicide-resistant crops	231–233
EPSPS transgene and other mutational effects in GE corn and their metabolic consequences cause endocrine disruptions.	Health effects of herbicides associated with herbicide-resistant crops	200–201
Glyphosate blocks the shikimate pathway; gut bacteria use this pathway to produce aromatic amino acids like L-Tryptophan, which is a precursor to serotonin and melatonin.	Health effects of herbicides associated with herbicide-resistant crops	231–233
Glyphosate is toxic to human cells.	Health effects of herbicides associated with herbicide-resistant crops	212–213

continued

TABLE F-1 Continued

	General Description	Page Number(s)
Glyphosate interferes with other metabolic pathways, including cytochrome P-450 pathway needed for proper liver detox.	Health effects of herbicides associated with herbicide-resistant crops	231–233
As a result of IARC's rigorous and independent review, the link between glyphosate and cancer has now been greatly strengthened. This toxic herbicide probably causes cancer in people. This new evidence of a serious health threat provides an additional justification for an urgent re-evaluation of glyphosate, separate and apart from the chemical's documented ecological harm, which in and of itself is sufficient to trigger immediate review and restrictions on use.	Health effects of herbicides associated with herbicide-resistant crops	208–213, 231–233
Exposure to 2,4-D will increase with the use of Enlist Duo because more 2,4-D will be in water, food, and air and be available for accidental ingestion.	Health effects of herbicides associated with herbicide-resistant crops	180–184
Glyphosate-resistant crops have new metabolites.	Health effects of herbicide-resistant crops	173–178
Four alternately spliced, overly long RNA transcripts were created with glyphosate-resistant soybean; these new proteins carry health risks.	Health effects of herbicide-resistant crops	233–235
RNAi-based GE crops do not produce a novel protein, but they may still present an ecological and food-safety risk. The "safeness" of the food may depend on the physiology of the consumer.	Health effects of RNAi technology	233–235, 416–419
Adjuvants in formulated pesticide mixtures are more toxic than the active ingredient(s) in the pesticide chemical. Acceptable daily intake thresholds for pesticides are therefore not valid because the intake thresholds only account for active ingredients, not adjuvants.	Appropriate animal testing	184–201
Gamma zein, a well-known allergenic protein, has been detected in MON810 corn. A number of seed storage proteins exhibited truncated forms.	Health effects of *Bt* crops	204–205

TABLE F-1 Continued

	General Description	Page Number(s)
Most serotonin is produced in the gut in response to tryptophan. Wheat is a good source of tryptophan, but when wheat is contaminated with glyphosate, the gut cells go into overdrive and begin producing too much serotonin, which in turn produces many of the common symptoms of celiac disease, such as diarrhea.	No herbicide-resistant wheat – not within the study's scope	217–218
Treating wheat with glyphosate just before harvest causes celiac disease. The glyphosate residue on the wheat gets in food and causes celiac disease because it will destroy the villi in the gut. Glyphosate also prevents the body from breaking down gliadin, a protein found in wheat.		At the time the committee was writing its report, there was no wheat with GE resistance to glyphosate.
Economic		
The dominance of GE varieties in the market has led to a decrease in private breeding programs, that is, a consolidation of industry.	Consolidation in agriculture	324–331
Seed company consolidation due to GE crops has caused the entrenchment of input-intensive monoculture farming systems based on propriety genetics.	Consolidation in agriculture	316–331
Seed company consolidation due to GE crops has driven up costs.	Consolidation in agriculture	324–327
Patent practices have locked up germplasm, both from competitors and from public-breeding programs. This has contributed to making non-GE seeds difficult to buy.	Genetic diversity in crop varieties	316–331
Seed company consolidation due to GE crops has narrowed farmers' seed options.	Genetic diversity in crop varieties	324–327
Reliance on glyphosate has created an expensive-to-fix problem in herbicide-resistant weeds. Reliance on *Bt* threatens to create a similar situation with insects.	Effects of insecticide and herbicide use	122–126, 136–139
Commitment to growing GE crops will eventually bar U.S. food and food products from other countries because the United States will not be compliant with labeling laws that will be adopted in most markets around the world.	Effects on global markets	306–310

continued

TABLE F-1 Continued

	General Description	Page Number(s)
Public and Social Goods		
Seed company consolidation due to GE crops allows a few companies to dominate the market, the result of which is products that are not technically superior or socially useful even if they are profitable.	Consolidation in agriculture	324–327
Seed company consolidation due to GE crops has further restricted the rights of farmers to save and exchange seed.	Seed saving	316–327
Genetic engineering has curtailed severely farmers' ability to breed and select their own seeds.	Seed saving	316–327
Seed company consolidation due to GE crops has skewed public sector R&D priorities.	Public sector research	327–331
Donor support for GE crop development shifts plant-breeding efforts in developing countries away from ongoing work in conventional plant breeding to genetic engineering. Research also shifts away from crops in which genetic engineering is not currently being pursued and away from agroecological improvement efforts.	Public sector research	283–287, 327–331
Historical public goods in agriculture, such as crop improvement for developing countries and specialty or minor crops, are moving into the realm of private goods because of patent protection of intellectual property. This change impacts the pace of research on these types of crops.	Public sector research Intellectual property	316–331
Farming with GE crops has caused or at least accelerated the deskilling of farmers in the United States and in developing countries that have adopted the crops.	Farmer knowledge	288–291
Social benefits of HR and *Bt* traits have been equivocal, variable, and uncertain. Productivity gains have been largely due to technologies and methods such as breeding rather than genetic engineering. Genetic engineering has contributed little so far to the response to climate change, to preserving biodiversity, to reducing pollution, and to conserving finite or scarce resources.	Effects of genetic engineering on yield Effects on landscape biodiversity	98–116, 127–133, 140, 331–333, 419–422
There have been negative effects on lives and cultures, especially those of indigenous peoples.	Effects on indigenous peoples	288–291

TABLE F-1 Continued

	General Description	Page Number(s)
Scientific Progress		
Seed company consolidation due to GE crops allows a few big companies to set the current priorities and future direction of agricultural research worldwide.	Consolidation in agriculture	324–327
Seed company consolidation due to GE crops has inhibited independent research.	Consolidation in agriculture	316–331
The shift to concentrating on molecular biology in the university system has depleted funds to public breeding programs.	Public sector research	327–331
Corporate support of university research makes public university scientists biased supporters of GE crops. The dramatic increase of private research funding of agriculture at universities, while public funding has been reduced, raises questions about the relationship between public and private genetic-engineering research agendas.	Public sector research	327–331
There is decreased access to and decreased public support for non-GE seed and indigenous seed because of GE seed.	Genetic diversity in crop varieties	318–319

TABLE F-2 Public Comments Regarding Potential Benefits of Genetically Engineered (GE) Crops and Their Accompanying Technologies

	General Description	Page Number(s)
Agronomic		
GE crops have contributed to increased production of soybean and corn globally.	Effects of genetic engineering on yield	98–104
GE rice with improved agronomic traits could deliver traits with consumer benefits.	Effects of Golden Rice	226–228, 283–285
Genetic disease resistance in crop seed is an easily deliverable, environmentally benign, and effective means of managing crop disease. Genetic disease resistance can be achieved by conventional breeding, but in some cases, genetically engineering resistance may be faster, more robust, or the only way possible to accomplish resistance.	Effects on plant disease	281–282, 406–408, 415–416
Environmental		
GE crops can contribute to increased production with reduced environmental impact.	Effects on environment Effects of genetic engineering on yield	98–104, 140–154
The use of GE crops has reduced the release of greenhouse gas emissions globally because of reduced tractor fuel use and additional soil carbon sequestration.	Effects on environment	152–154, 420
Genetic engineering can be used cost-effectively to increase nutrient-use efficiency and resilience to climate change.	Effects on environment	422–425
GE trees may be the best approach to combatting disease and pest pressure on trees that may increase because of climate change.	Effects on environment	412–415
GE varieties have transformed American agriculture, helping U.S. farmers remain internationally competitive while reducing costs and promoting important environmental and sustainability goals.	Effects on landscape biodiversity U.S. socioeconomic effects	256–270
Returning blight-resistant American chestnut (through genetic engineering) to eastern forests, especially on private land, can help restore the structure and function of these forests.	Effects on landscape biodiversity	412–415
GE methods provide one way that science can combat the decline and eventual extinction of ecologically important species like trees.	Effects on landscape biodiversity	412–415

TABLE F-2 Continued

	General Description	Page Number(s)
Genetic engineering, as in the case of the American chestnut, has the ability to correct for invasive diseases that wipe out native species (e.g., trees) and repair a biome.	Effects on landscape biodiversity	412–415
Northeast forests are losing all of their ash and hemlock trees to invasive insects. In some areas of the native forest, tent caterpillars have devastated sugar maples and, if the Asian longhorned beetle becomes widely-distributed, forest cover will be reduced by more than 50%. GE trees must be a part of the defense against such a tragic outcome. GE American chestnut is particularly important because of this tree's tremendous benefit to wildlife.	Effects on landscape biodiversity	412–415
The wood of the American chestnut is beautiful, strong, and rot resistant. Unlike oak, the tree produces a mast crop every year for wildlife. The ecosystem is not the same without it. Genetic engineering is the key to bringing the species back from the brink. We are not going to achieve recovery by relying on breeding these trees with resistant relatives.	Effects on landscape biodiversity	412–415
Adoption of GE crops has reduced the amount of pesticide sprayed globally.	Effects of insecticide and herbicide use	108, 116–121, 133–135
The use of glyphosate and glyphosate-resistant crops replaced the use of more hazardous herbicides in terms of pounds of active ingredients used.	Effects of insecticide and herbicide use	133–135
Herbicide-resistant crops have facilitated the expansion of conservation tillage, helping to reduce soil erosion.	Effects on soil health and runoff	152–154
Human Health and Food Safety		
Regulatory delays of second-generation GE crops have created a cost to productivity and to human health.		310–316
GE cotton has increased yields in India, leading to fewer suicides.	Effects of genetic engineering on yield Socioeconomic effects in developing countries	111–114

continued

TABLE F-2 Continued

	General Description	Page Number(s)
Reductions in aflatoxin and fumonisin contamination have been documented in field studies of *Bt* corn due to reduced insect injury to corn kernels. This is particularly the case under conditions moderately to highly favorable for ear rot and mycotoxin contamination.	Health effects of *Bt* crops	229–231
Economic		
GE crops have created net economic benefits at the farm level amounting to $18.8 billion in 2012 and $116.6 billion of 17 years (in nominal terms). Economic gains are split 50/50 between farmers in developed countries and farmers in developing countries.	Effects on farmers in developed and developing countries	256–287
GE crops under development in some African countries, such as black sigatoka resistant banana in Uganda and maruca-resistant cowpea in Ghana, will help improve the livelihood of smallholder farmers because this kind of technology is relevant to their needs and interests. To be effective, it also needs to be affordable, accessible, and profitable.	Effects on farmers in developing countries	283–285
The aggregated global benefits of GE rice are estimated to be valued at $64 billion per year.	Effects of Golden Rice	226–228
Public and Social Goods		
Genetic engineering is useful because it can make possible some breakthrough advances in crop variety improvement for some orphan crops or crops of importance to developing country farmers that conventional processes could not reach.	Socioeconomic effects in developing countries	405–408
Bringing technology like genetic engineering to agriculture in some African countries will make farming modern and more profitable, which will make a profession in agriculture more attractive to young people and stem the flow of migration out of rural areas.	Socioeconomic effects in developing countries	271–287
Study after study has shown GE crops to be safe for consumption. In the case of trees, they could help save an industry (citrus greening) and help repopulate a beloved native species (American chestnut).	Socioeconomic effects	225, 412–415

TABLE F-2 Continued

	General Description	Page Number(s)
Scientific Progress		
Directly manipulating gene expression in combination with “ask the organism” experimental designs provides the fastest way forward to understanding how nature works.		417
Genetic engineering is useful for trees because of their long-breeding cycle, the difficulty of introgressing new genes, and the challenges in identifying dominant genes. It can deliver diverse traits to tree variety development.	Special concerns with trees	412–419
Traditional breeding is tedious and time-consuming for trees. Genetically engineered American chestnut is a much faster and surer way to bring back a valuable species.	Special concerns with trees	405–410

TABLE F-3 Public Comments Offering Suggestions or Raising Questions About Genetically Engineered (GE) Crops and Their Accompanying Technologies

	General Description	Page Number(s)
Environmental		
Genetic engineering is one of the safest and environmentally beneficial technologies available to mankind and it is important that it is used widely to the benefit of man and nature.	Effects on environment	140–154, 236–237
In order to cope with increasingly complex and severe environmental problems, all options need to be assessed dispassionately and not muddied with emotional appeals based on fear and ignorance.	Effects on product development	508–513
Peer-reviewed scientific studies have demonstrated that genetic-engineering processes are safe. The alternative of pesticide and fungicides will be more detrimental to the environment and people.	Effects on environment Effects of insecticide and herbicide use Health effects of *Bt* crops Health effects of herbicide-resistant crops	116–121, 133–135, 184–207, 236–237
EPA needs to put a system in place that proactively detects and then remediates populations of resistant insects.	Effects of insect and weed resistance	122–126
EPA should mandate herbicide resistance management and provide incentives for integrated weed management.	Effects of insect and weed resistance	136–139
The American chestnut is a species that provides high quality wood. Its absence for a century has left a void in the ecology and food chains of U.S. eastern forests. The loss of this species was an almost incomprehensible ecological loss of which most people are unaware.	Effects on landscape biodiversity	412–415
GE may be favored over other promising methods or systems like conventional breeding and agroecology by policy-makers because it is seen as more profitable to the industry. For example, agroecological methods typically are less dependent on purchase inputs like seed, fertilizers, or pesticides than industrial agriculture.	Comparison to non-GE systems	283–287

TABLE F-3 Continued

	General Description	Page Number(s)
The opportunity cost of not considering sound agroecological and other proven sustainable small scale and locally productive farming methods (perhaps better suited to many smaller African and Asian farmers) should not be overlooked.	Comparison to non-GE systems Farmer knowledge	283–287
Funding for GE crop development often comes without funding for complementary longer-term interventions. Agroecological and farm management interventions are prerequisites for the introduction of technologies like genetic engineering, but they are often underfunded and neglected.	Comparison to non-GE systems	283–287, 331–333
Agroecology is sometimes presented as an alternative to crop improvement via genetic engineering. These do not have to be an "either-or." There is no reason that GE traits cannot be introgressed into local crop varieties that might be used in an agroecological farming system.	Comparison to non-GE systems Farmer knowledge	283–291
Human Health and Food Safety		
FDA's review of GE crops is not sufficiently adequate to alleviate health concerns. FDA's reviews are not comprehensive.	FDA regulatory actions	184–207, 466–477
FDA's current approach may not sufficiently address the safety of imported products made from GE crops.	FDA regulatory actions	184–207, 466–477
FDA should require premarket safety assessments for all GE crops, including stacked trait varieties.	FDA regulatory actions	466–477, 508–513
GE trait, crop, and food testing methods and results are inherently suspect because all studies are carried out by the technology developers or their contractors. The details of these studies are not published, and full sequence information is not disclosed. GE trait patent holders often impose limits on who can conduct science on their seeds and traits and malign scientists who report findings that raise questions about GE trait or crop safety or performance.	Bias in testing of GE crops and food	184–207, 316–331
No government funding is provided to independent scientists to evaluate GE crop and food safety.	Bias in testing of GE crops and food	171, 184–207
Industry supports most of the studies of GE crops and foods; therefore, these results cannot be trusted.	Bias in testing of GE crops and food	171, 184–207

continued

TABLE F-3 Continued

	General Description	Page Number(s)
The majority of nutritional studies conducted on GE crops do not assess health effects, concentrating instead on animal weight gain or milk or egg production.	Sufficiency of health testing	176–207
No study has tested whether there are unique human health and environmental risks associated with stacked-trait GE cultivars. Most GE foods now contain multiple stacked traits with multiple promoter genes and regulatory sequences. This fundamental change leads to novel and more complex ways in which environmental conditions can alter gene expression patterns and the presence and levels of novel toxins and allergens.	Sufficiency of health testing	176–207, 464–493
One or more of the GE traits in almost all of today's GE corn and soybean varieties has not been analyzed or addressed in any health studies published in peer-reviewed journals.	Sufficiency of health testing	176–207
The dose levels of *Bt* are not adequately evaluated by EPA in foods like *Bt* sweet corn and *Bt* eggplant. No study has been done on the impacts of transgene and *Bt* proteins in GE eggplant on human reproductive outcomes and neurological development.	Sufficiency of health testing	176–225
New GE-traited food for human consumption should have full 'omics' molecular profiling performed as well as siRNA/miRNA profiling to determine differences between GE and isogenic non-GE variety grown in the same location at the same time. Such data would rule out the presence of potential toxins, allergens, and compositional/nutritional disturbances caused by GE transformation. There should be 2-year feeding studies in rats and/or mice, followed by large farm animal toxicity studies, and then human dose escalation trials. Such testing should be paid for by the government.	Sufficiency of health testing	200–201
There are no proven and reliable animal models to detect new, food-based human allergens, so GE foods would have to be tested on human volunteers to find new and unexpected allergens.	Sufficiency of health testing Appropriate animal testing	202–207
Current allergy testing is not rigorous enough.	Sufficiency of health testing	202–207
GE crops and food negatively affect everyone, but particularly those with chronic health conditions.	Sufficiency of health testing	202–225

TABLE F-3 Continued

	General Description	Page Number(s)
A high concentration of GE *Bt* toxins in food has not previously been a part of the human or animal diet and their impact on GI tract health and its possibility to be an antinutrient have not been researched.	Sufficiency of health testing	215–225
Glyphosate has not been tested or assessed for long-term safety for regulatory purposes. Independent studies show it is highly toxic to animals and humans.	Sufficiency of health testing	212–213, 231–233
The impacts of GE crops/food on the gut bacteria (horizontal gene transfer, antibiotic effects of glyphosate, block production of aromatic amino acids, etc.) and their impact on the health of individuals and newborns is unclear.	Sufficiency of health testing	221–225
GE crop test sites should be publicly posted. Contamination of conventional and organic crops puts farmer livelihood at risk as well as risking allergic and toxic impacts to the general population that also severely handicaps their doctors' ability to diagnose.	Sufficiency of health testing Coexistence of GE and non-GE crops	176–225, 296–302
There are few if any chronic studies (2-year feeding trials, multigenerational studies) that have been done in rats, mice, or other species that had to be done to uncover a risk that was not suspected due to similarity to known toxins. And many of the studies that are being submitted to journals like *Food and Chemical Toxicology* and *Regulatory Toxicology and Pharmacology* have significant design problems and the results are not fully reliable especially for characterizing human risks. Often the test materials are not well characterized, inappropriate controls are used and the publications report "statistically significant differences" without any measure or certainty about the biological relevance of the data. Thus the studies should and must be questioned in terms of relevance to human food safety. We need to use first principles of science before we demand a lot of unnecessary, expensive, and potentially confounding testing on products that are scientifically relatively easy to evaluate.	Sufficiency of health testing	184–198

continued

TABLE F-3 Continued

	General Description	Page Number(s)
A review of proper peer-reviewed literature on GE crops reveals a long history of safety and utility. It has been documented that many billions of animals worldwide over many years have consumed GE feed, and no effect on the health of these animals has been detected. It is very telling that so many animals over such a long time have been eating GE feeds. There is no reasonable way to discount this hugely important fact.	Sufficiency of health testing	195–198
There should be post-approval surveillance monitoring (as called for in the 2004 NRC report).	USDA regulatory actions	202–207, 464–493
There needs to be safety assessment protocols for double-stranded RNA.	Health effects of RNAi technology	233–235, 359–360, 416–419
The GE crop system (including seeds and coatings, pesticides and inert ingredients, and study findings hidden behind Intellectual Property Rights barriers) should not be framed in a way that suggests local regulation will be a hindrance to transgenic crops whilst paying lip service to robust risk assessment and transparency of transgenic study data to the public at large.	Effects of debate about genetic engineering	5–28
Economic		
A recent industry-sponsored study found that the average cost to develop a trait through GE was about $136 million (mostly from R&D rather than regulatory costs), while development of typical traits using conventional breeding was about $1 million for grain crops.	Cost of research and development Cost of regulation	310–316
Regrowth of the American chestnut would be a major boost to the furniture and lumber industry.	U.S. socioeconomic effects	412–415
Public and Social Goods		
Often quick scientific assessments in developing countries are used to bolster larger claims about the usefulness of genetically engineered crops to farmers in those countries.	Socioeconomic effects in developing countries	257–287
More effort needs to be devoted to understanding, over the course of time, which demographic groups in developing countries benefit from the introduction of GE crops.	Socioeconomic effects in developing countries	271–287, 291–294

TABLE F-3 Continued

	General Description	Page Number(s)
It has been documented that the adoption of *Bt* cotton in Colombia was received favorably by women because it reduced the number of laborers they had to hire to spray pesticides.	Socioeconomic effects in developing countries	291–293
Agricultural biotechnology can improve productivity, secure and improve yield, and produce higher quality crops. It is critical to the sustainability of agriculture. If food production is to increase to meet projected population rises over the next generation, genetic modification and other biotechnologies should be available to growers as an option.	Feeding the growing world population	331–333, 437–442
Socioeconomic controversies have lowered the long-term potential for GE to advance sustainable agriculture and ensure food safety.	Effects of debate about genetic engineering	302–331, 436–442
Lack of public-sector support for applied research in genetic engineering hinders the number and types of traits developed.	Public sector research	283–287, 327–331
The monopolistic powers that create and market GE seeds have disingenuous motives.	Consolidation in agriculture	316–331
After over a decade of development, Golden Rice has lower yields than comparable rice and has not yet been shown to address vitamin A deficiencies under community conditions.	Effects of Golden Rice	226–228, 432–436
Access to Information		
Food-safety agencies and authorities and private companies do not publish raw data of their studies.	Transparency in data reporting	502–506
Locations of test plots should not be kept secret from farmers whose crops, markets, and communities could be harmed by their proximity to these plots.	Transparency Coexistence of GE and non-GE crops	296–302, 502–506
USDA should require sequence information for all field trials.	Transparency Regulation of GE crops	466–477, 508–510
Confining the debate on GE crops to peer-reviewed literature is elitist.	Data quality and comprehensiveness	37–44
Lack of labeling takes away consumer choice.	Public right to know	303–306, 462, 501

continued

TABLE F-3 Continued

	General Description	Page Number(s)
Is it scientifically justified for some GE crops to be regulated because of Agrobacterium transformation but not if the transformation is made with a gene gun?	Regulation of genome editing	466–477, 493–500
Intellectual property protection for GE crops is important to encourage investment in crop development and ensure their best use for agriculture. Patent protection can be used to block competitors, but it can also be used to promote broad use of technologies because it encourages inventors to bring forth new ideas by providing the security that these ideas will be protected.	Intellectual property	316–324
The biggest issue with GE crops is the surrounding policy and patent abuse, not the underlying science itself.	Intellectual property Cost of regulation	316–324
Scientific Progress		
The frequency of transformation-induced mutations and their importance as potential biosafety hazards are poorly understood.	Unintended effects of genetic engineering	378–395
Genetic engineering is unnecessary meddling with Mother Nature.	Ethics of genetic engineering	65–73
Marker-assisted selection (MAS) breeding can achieve the same claims as genetic engineering without the drawbacks. The low number of commercialized GE traits is evidence that the technology is not that successful and is therefore not needed because conventional breeding and MAS breeding can get better results on a faster timescale.	Effects of genetic engineering on yield Comparison to non-GE systems	354–357, 405–408
The genomes of living things code for many thousands of proteins, and alteration or addition of a single gene does not create some freakish hybrid. It also does not change the basic nature of the plant itself.	Ethics of genetic engineering	65–73, 406–408
Diseases have devastated (chestnuts) and are devastating trees (e.g., citrus greening). Modern breeding can assist in controlling these diseases and protecting the diversity and health of tree species and forests.	Effects on plant disease	412–419

TABLE F-3 Continued

	General Description	Page Number(s)
Efficiency and efficacy of RNAi differ among species, mode of delivery, and genes targeted. There is currently limited capacity to predict the ideal experimental strategy for RNAi directed at a particular insect because of an incomplete understanding of how the RNAi signal is amplified and spread among insect cells.	RNAi	416–419
Changing the nature, kind, and quantity of particular regulatory-RNA molecules through genetic engineering can create biosafety risks. While some GE crops are intended to produce new regulatory-RNA molecules, these may also occur in other GE crops not intended to express them.	RNAi	233–235, 359–360, 416–419
Genome editing is creating indistinct boundaries in existing government regulations of GE crops.	Regulation of GE crops	493–500

Appendix G

Glossary

Actor	A social scientific concept used to refer to individuals or collective entities (for example, government agencies, firms, retail groups, nonprofit organizations, and citizens) when their behavior is intentional and interactive
Adventitious presence	The unintended and accidental presence of low levels of GE traits in seeds, grains, or foods
Allele	One of the variant forms of a gene at a particular location (that is, locus) on a chromosome. Different alleles produce variation in inherited characteristics, such as blood type
Antinutrient	A compound (in food) that inhibits the normal uptake or utilization of nutrients or that is toxic in itself
Antisense	A complementary RNA sequence that binds to (and thus blocks the transcription of) a naturally-occurring (sense) messenger RNA molecule
Biotechnology	A number of methods other than selective breeding and sexually crossing plants to endow new characteristics in organisms

Cassette	A sequence of DNA with one or more genes of interest and with their respective promoters for expression, typically flanked by a set of sequences that facilitate insertion and selection into the genome of a recipient organism
Cisgenic plant	A plant that is genetically engineered with an endogenous gene from a sexually compatible species, that is, a transfer that could be accomplished through conventional plant breeding
Coexistence	To exist together or at the same time. In the context of the report, farms with GE and non-GE crops existing together
Conventional plant breeding	Modification of the genetic constitution of a plant through sexually crossing different genomes or mutagenizing a plant's genome with chemical methods or irradiation, and selecting desirable plants to serve as parent lines
CRISPR (clustered regularly interspaced palindromic repeats)	A naturally occurring mechanism of immunity to viruses found in bacteria that involves identification and degradation of foreign DNA. This natural mechanism has been manipulated by researchers to develop gene editing techniques
Crop	Vascular plants that are grown for subsistence, environmental enhancement, or economic profit
De novo genome sequencing	Determination of the DNA sequence of the genome (full genetic complement) of an organism
Deskilling	The appropriation of labor whereby industry effectively eliminates skilled workers by introducing new technologies that defray labor costs and increase profits
Doubled-stranded RNA (dsRNA)	Two RNA molecules that are bound to each other by complementary base pairing
Endogenous	A naturally occurring substance or feature

Epigenome	The physical factors affecting the expression of genes without affecting the actual DNA sequence of the genome
Epigenomics	Study of the epigenome using high throughput technologies
Eukaryote	An organism with membrane-bound organelles including the DNA-containing nucleus, mitochondrion, and in plants, the plastid
Event	A unique genetically engineered plant line that is characterized by the location of the transgene in the plant genome
Expression	The result of a gene being transcribed into RNA and ultimately conferring a trait
Gene drive	A system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. Thus, the result of a gene drive is the preferential increase of a specific *genotype*, the genetic makeup of an organism that determines a specific *phenotype* (trait), from one generation to the next, and potentially throughout the population
Genetic engineering	The introduction or change of DNA, RNA, or proteins by human manipulation to effect a change in an organism's genome or epigenome
Genetic modification	The process used to modify the genome of an organism
Genetically modified	Refers to an organism whose genotype has been altered and includes alteration by genetic engineering and nongenetic engineering methods
Genome	The complete sequence of the DNA in an organism
Genome editing	Specific modification of the DNA of an organism to create mutations or introduce new alleles or new genes

Genomics	The study of the genome which typically involves sequencing the genome and identifying genes and their functions
Genotype	The genetic identity of an individual. Genotype often is evident by outward characteristics
Germplasm	The available set of accessions that represent genetic diversity for a species and are used for breeding including cultivars, landraces, and wild species relatives
Glyphosate	A herbicide widely used and marketed as RoundUp®
Gross income	The total income, both cash and non-cash, received by a farm or business before any expenses are paid
Gross margin	The difference between gross income and variable costs
Homology-directed repair	A naturally occurring mechanism for repair of a DNA sequence in a cell that has a double strand break. This repair mechanism uses the DNA from a homologous chromosome or artificially added DNA with homologous sequence to the DNA that has the break as a template for the repair
Household income	A measure of the combined incomes of all people sharing a particular household or place of residence. It includes every form of income, for example, salaries and wages, retirement income, near-cash government transfers (for example, food stamps), and investment gains
Integrated pest management	A pest control strategy based on the determination of an economic threshold that indicates when a pest population is approaching the level at which control measures are necessary to prevent a decline in net returns. In principle, IPM is an ecologically based strategy that relies on natural mortality factors, such as natural enemies, weather, and crop management, and seeks control tactics that disrupt these factors as little as possible

Intragenic plant	A plant that is genetically engineered with various plant DNAs, all of which come from varieties of the plant or sexually compatible relatives that are combined into a gene and then inserted into the genome
Isoline	An individual that differs genetically from another by only a small number of genetic loci
Landraces	A collection of accessions of a crop species that were developed and maintained by traditional farmers. They are typically not as genetically uniform as modern commercial cultivars and often have traits of interest to local farming communities
Marker-assisted selection	The use of DNA sequences to determine which plants or organisms have particular version (allele) of existing genes. Markers do not become part of the plant's genome
Messenger RNA (mRNA)	A nucleic acid molecule that is transcribed from DNA and provides instructions to the cell's translational machinery to produce specific proteins
Metabolomics	Systematic global analysis of nonpeptide small molecules, such as vitamins, sugars, hormones, fatty acids, and other metabolites. It is distinct from traditional analyses that target only individual metabolites or pathways
Net farm income	The difference between total revenue and total expenses, including gain or loss on the sale of capital assets
Net return	Gross income minus a set of expenses. It is usually estimated for a specific resource
Nonhomologous end joining	A naturally occurring mechanism in which DNA molecules with double strand breaks are repaired. Typically results in insertions and deletions

Nucleotide	One of the four repeating subunits of DNA and RNA that consists of a five-carbon sugar, phosphoric acid, and an organic base that contains nitrogen. The nucleotides are adenine, guanine, cytosine, and thymine for DNA; uracil substitutes for thymine in RNA
Phenotype/Phenotypic	The visible and/or measurable characteristics of an organism (i.e., how it appears outwardly and physiologically) as opposed to its genotype, or genetic characteristics
Plasmid vector	A circular DNA molecule endogenous to bacteria that is used to replicate and transfer DNA to new cells
Plastome	The genome of plastids such as the chloroplasts
Post-transcriptional modification	Modification of a mRNA after it is synthesized
Profit	Gross income less expenses
Prokaryote	An organism that lacks membrane bound organelles
Proteomics	The analysis of the complete complements of proteins. Proteomics includes not only the identification and quantification of proteins, but also the determination of their localization, modifications, interactions, and activities
Quantitative trait locus (QTL)	A region of the genome that contributes to a phenotype in a quantitative manner
Reagent	Generally a chemical used in a science experiment; in the context of genome editing, a chemical that is used to modify DNA
Recombinant DNA	Any novel DNA sequence created using genetic engineering

Reference genome	The DNA sequence from a single individual of a species that is used as a reference in subsequent sequencing of other individuals
Refuge (plural = refugia)	A place protected from danger. In the context of the report, a part of a farm or field where the crop does not produce insecticidal toxins, where a pest with a toxin-susceptible genotype can survive
Resequencing	Generation of whole genome shotgun sequences of individuals that are overlaid on a reference genome
Revenue	See Gross income
RNA interference (RNAi)	A natural mechanism found in nearly all organisms in which the levels of transcripts are reduced or suppressed
Single nucleotide polymorphism (SNP)	Variation in a single DNA base pair that occurs at a specific position in the genome
Small interfering RNA (siRNA)	RNA molecules that function in RNA interference
Somaclonal variation	Epigenetic or genetic changes, sometimes expressed as a new trait, resulting from in vitro culture of higher plants
Synthetic biology	The ability to generate novel traits or organisms using synthetic genes or by bringing together genes from multiple organisms. Also defined as the ability to generate novel traits or organisms using computationally designed DNA or reagents that are not directly found in nature
TILLING (targeting induced local lesions in genomes)	A method to efficiently screen for a specific mutation within a population of mutagenized plants
Trait	A genetically determined characteristic or condition that is the target of plant breeders and important in crop production

Transcriptomics	The study of transcripts including the number, type, and modification; many of which can impact phenotype
Transgene	Any gene transferred into an organism by genetic engineering
Transgenic organism	An organism that has had genes that contain sequences from another species or synthetic sequences introduced into its genome by genetic engineering
Variety	A specific accession of a crop species that has been bred for improved agronomic traits variety that has been intentionally selected for specific phenotypic features such as yield. Crops that are typically sold and planted are cultivars
Yield drag	Yield drag is a reduction in yield potential owing to the insertion or positional effect of a transgene. Yield drag can be overcome by increased effort in conventional breeding to increase yield of the cultivar to balance out effects of yield drag
Yield lag	A cultivar with a transgene has a tendency to initially yield lower than elite cultivars without the novel traits because of yield-reducing genes that have accompanied the transgene due to genetic linkage. Over time, the yield lag usually disappears as the transgene is genetically separated from the yield reducing genes