WRI WHITE PAPER

DESIGNING GENES

Aiming for Safety and Sustainability in U.S. Agriculture and Biotechnology

DON S. DOERING

WORLD RESOURCES INSTITUTE

WASHINGTON, DC

KAREN HOLMES
EDITOR

HYACINTH BILLINGS
PUBLICATIONS DIRECTOR

MAGGIE POWELL
LAYOUT

ISBN 1-56973-557-3

Printed in the United States of America on chlorine-free paper with recycled content of 50%, 20% of which is post-consumer.

Contents

Acknowledgments

WRI gratefully acknowledges The Joyce Foundation for its generous support of this publication. The author gratefully acknowledges colleagues at WRI for helpful discussions; Sarah Bellos and Liz Moss for research assistance; David Jhirad, Suzie Greenhalgh, Al Hammond, Siet Meijer, and Rob Wolcott, for review and revision of the manuscript; Paul Faeth and Liz Cook for support of this publication; and Winrock International for support. The author and World Resources Institute extend our thanks to the reviewers of the manuscript, Kate Clancy, Helmut Gaugitsch, Greg Jaffe, and Julia A. Moore; the manuscript does not necessarily reflect their views. The author also acknowledges Karen Holmes and Robert Livernash for their excellent work on editing and improving the manuscript.

While recognizing the contributions of those mentioned above, the author retains sole responsibility for the opinions expressed in this report.

Executive Summary

The health and productivity of agriculture is vital to U.S. national interests. Current agricultural practices, however, carry serious environmental and economic costs, making a shift toward sustainable alternatives imperative for U.S. agriculture. Modern agricultural production is based on heavy use of irrigation, energy, and chemical inputs (pesticides, herbicides, and fertilizers) that degrade the environment and impose considerable economic burdens on current and future generations. Most commodity farming in the United States relies on high levels of synthetic chemical inputs and only modest use of crop rotations and conservation tillage. Agricultural practices increase greenhouse gas concentrations by adding carbon dioxide, methane, and nitrogen oxides to the atmosphere, contributing to the threat of global climate change. National policies to reduce food prices and expand agricultural exports through subsidies and high production levels have also taken their toll on farm profitability over the last half century, with most U.S. agricultural production now carried out at or near economic loss.

In this context of unsustainable agriculture, genetically engineered (GE) crops have become a major feature of current U.S. agricultural practice whose value and desirability is hotly debated. U.S. farmers strongly prefer the GE varieties of many principal commodity crops, including corn (45 percent of the annual crop), cotton (76 percent of the annual upland cotton crop), and soy (85 percent of the annual crop). Crops genetically engineered for herbicide tolerance and insect resistance are now planted on over 110 million acres of soybeans, corn, and cotton in the United States. Scientific assessments show that GE approaches to crop improvement generate potential benefits in many arenas of agricultural performance, including reduced volume and toxicity of agricultural chemical use, increased prevalence of conservation tillage and no-till practices, and simplified farm management.

However, many areas of scientific uncertainty and public unease remain regarding today's GE crop varieties and those of tomorrow. Public opposition to current GE crops has developed because of concerns about environmental and health hazards as well as objections to the agricultural, economic, and political system in which GE crops have been developed, marketed, and regulated. The extraordinary pace of technical innovation and farmer adoption of GE crops has put policy-makers in a reactive mode—often one step behind new technologies and emerging environmental and social concerns. Prominently absent from the debate about GE crops is a long-term research and development (R&D) agenda that connects the present challenges and future goals of agriculture to those of genetic engineering.

A DESIGN APPROACH TO GE CROPS: INTEGRATING SUSTAINABILITY INTO POLICY, RESEARCH, AND INVESTMENT FOR CROP BIOTECHNOLOGY

How does genetic engineering fit into long-term goals for U.S. agriculture? Seldom is this fundamentally important question asked, much less answered.

This paper explores the intersection of two critical but rarely juxtaposed science and policy issues: the future of GE crops and the path to agricultural sustainability. The discussion focuses on the Midwestern United States—home to approximately 60 percent of U.S. commodity crop production and the birthplace of the world's first commercial GE crops. As the environmental, economic, and social problems wrought by unsustainable agricultural practices become more acute in the Midwest and elsewhere in the United States, targeting policies for and investments in GE crop research and development toward such goals as soil conservation, safe water, habitat protection, healthy food, and profitable farms becomes ever more crucial. *Designing Genes* is intended to stimulate discussion of the connection between key issues of genetic engineering and the long-term future of U.S. agriculture. It also aims to catalyze action to integrate biotechnology policy and investments with plans for shifting U.S. agriculture onto a path toward sustainability.

Genetic engineering and other techniques of modern biotechnology are moving crop improvement firmly into a new realm of product design. Opponents and proponents alike have debated the environmental, economic, and social impacts of GE crops in the context of proposals and strategies—such as new regulatory structures, labeling laws, growers' agreements, and intellectual property rules—aimed at the end of the product pipeline. While such end-of-pipe measures are the only options for current products, upstream design goals for safety and sustainability can raise the value of future GE crops by inspiring research and innovation, reducing negative health and environmental impacts, and increasing the social acceptance and social utility of biotechnology.

TWO DESIGN GOALS: *INCREASE SAFETY* AND *CREATE LONG-TERM VALUE*

Two upstream design goals are of central importance for research and development of GE crops: *design-for-safety* and *design-for-sustainability*.

- **Design-for-safety focuses on concerns inherent to genetic engineering that can be approached through improved design,** such as increasing the precision of gene insertion, limiting inserted genes to just the necessary DNA sequences, controlling when and where those genes are turned on, and preventing new genes from moving elsewhere in the genome of the target species or into the genomes of related species. Design-for-safety addresses human and environmental safety and reducing the probability of unintended consequences. GE crop designs that increase measurable and perceived product safety could potentially reduce regulatory costs, lower future liabilities for farmers and agricultural technology developers, and open market opportunities. Design-for-safety represents an integral step toward the second goal, design-for-sustainability.
- **Design-for-sustainability targets reductions in the environmental impacts of agriculture and increases in crop and natural biodiversity, economic growth, nutrition of foods, and the societal benefits of agriculture.** Design-for-sustainability encompasses the development of traits that improve crop performance in such areas as resistance to pests and diseases and utilization of water and nutrients—characteristics that also promote environmental protection through reduced use of chemicals, energy, and water. Other GE design goals that support a shift toward agricultural sustainability include the development of traits for improved nutritional content of food and feed crops, plant-based production of chemicals and industrial materials, and bioremediation of contaminated soils. Design-for-sustainability goals offer important potential opportunities to increase farm income and competitively reposition U.S. agriculture in global markets.

CLOSING GAPS AND DEVELOPING A NEW R&D AND POLICY AGENDA

At the heart of efforts to create an R&D agenda for genetic engineering and agricultural sustainability must be a rigorous and participatory process involving key stakeholders. To build a compelling political, social, and economic case that influences both public and corporate policy, a multi-stakeholder, multi-expert analytic process should be undertaken to produce a clear R&D agenda, the science policy to support that agenda, and a broad policy agenda to spur market development, create incentives for innovation, and ensure social value.

Four elements are proposed in this white paper for a process to integrate policy and investment in crop genetic engineering for agricultural sustainability: problems and goals analysis, scenario planning of U.S. agricultural futures, trait value analysis, and a technology roadmap.

- The first step, a quantitative, comprehensive goals analysis, should include specific targets and indicators of agricultural sustainability.
- Second, scenario analysis involves a multi-expert process to develop detailed narratives of multiple plausible futures for U.S. agriculture. The role of GE crops, priorities for research, and necessary enabling policies can be back-cast from each future scenario. Scenarios set in about 2015 would be in a

period beyond current research grants, the current Farm Bill, and corporate product pipelines, but near enough to influence policy and investment. The analysis should include some scenarios that do not rely on GE crops but upon other approaches to agricultural sustainability goals.

- The third proposed element, trait value analysis, entails estimating, measuring, and modeling the risks, benefits, and likely technical realization of various GE crop traits. Estimates of the impact of any particular trait improvement must be considered under different cultivation conditions and in different policy contexts, and also must be compared to alternative approaches. For example, a trait that improves nitrogen utilization might only be economically preferable at a certain threshold level of fertilizer price and/or cost of nutrient pollution management.
- Finally, the previous steps of defining problems and goals, developing future scenarios, and analyzing the value of specific traits should be used to create a technology roadmap to guide R&D priorities. Technology roadmapping is a process as well as a product that should engage experts from multiple disciplines to identify technical gaps and critical enabling technologies needed to meet sustainability goals.

CONCLUSIONS AND RECOMMENDATIONS

Policies and additional research and investment are needed to ensure that the role of genetic engineering in the future of U.S. agriculture supports economic, environmental, and social well-being. The potential of chemical-intensive agriculture, integrated agriculture, organic agriculture, or biotechnology-based agriculture to meet future human needs is hotly debated, but is not well-informed by a strongly substantiated, data-driven analysis of relative future costs, risks, and benefits, such as the one that would emerge from the process described above. Markets for GE crops designed for sustainability will only develop with appropriate planning and broad participation within a favorable policy context of trusted regulatory agencies, incentives for more sustainable agriculture, and research investment toward long- term goals.

The political barriers to creating an R&D agenda and policy environment that promotes the safety and sustainability contributions of GE crops are considerable. Established agricultural interests are reluctant to acknowledge the unsustainable aspects of U.S. agriculture in general and Midwestern agriculture in particular, especially the impacts of subsidies, over-production, and chemical inputs. The leading agricultural biotechnology companies are also agro- chemical companies and thus are reluctant to directly address the risks of chemically intensive agriculture. The intellectual property environment in the United States is designed for the appropriation of publicly developed technologies by private commercial interests and may not favor investment in technologies for public needs for which there are not yet markets.

Despite these obstacles, powerful shared interests are primed to motivate actors in the public and private sectors to partner in pursuit of sustainable agriculture goals. A better coordinated national R&D policy for agriculture and genetic engineering is needed—one that reflects what society most needs agriculture to accomplish, is guided by goals of agricultural sustainability, and presents a vision of a U.S. agricultural future that diverse sectors of society can align behind.

To plan for and take action to integrate genetic engineering with the goals of sustainable agriculture, this paper outlines recommendations for key stakeholder groups.

- **National agriculture R&D strategies should be strengthened by incorporating targets for agricultural sustainability. Inter-agency cooperation among those charged with scientific assessment, basic research, and applied agricultural research and technology development should be a prominent feature of such strategies.** For the agencies that regulate biotechnology—the U.S. Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration—there is an enormous need and opportunity for increased research coordination as well as restructuring and expansion. There is a similar opportunity for research coordination and shared goals among the agencies that fund basic research and technology development in plant molecular genetics, ecology, and environmental studies, including the National Institutes of Health, the National Science Foundation, and the Department of Energy.

- **Agricultural biotechnology companies should provide technical and political support for development of a research agenda and a policy agenda for integrating genetic engineering with the goals of a transition to sustainable agriculture.** These companies have a significant stake in partnering in a strong public-sector initiative that efficiently and transparently addresses safety and sustainability concerns about GE crops. Upstream efforts to improve design-for-safety and design-for-sustainability of GE crops are likely to benefit biotech companies by lowering product development and regulatory costs, shortening the time to market, boosting public acceptance of GE products, and reducing future corporate liabilities.
- **U.S. farmers and agricultural trade interests should lend their support to policies and research linking crop genetic engineering and agricultural sustainability.** Crops with built-in mechanisms for environmental safety and sustainability could help open global markets to export crops and differentiate U.S. products from low-cost commodity production. With their long-term interest in the stewardship of land and water resources, farmers and agricultural trade interests can provide a powerful voice for design-for-safety and design-for- sustainability goals of policy and investment in R&D for GE crops.
- **The basic research community has an opportunity to provide leadership and an independent voice for discovery and innovation to integrate genetic engineering and the long-term goals of U.S. agriculture.** Basic research often flourishes where scientific investigation becomes aligned with important social and economic goals, such as the setting of national goals to eradicate polio, explore the outer reaches of the solar system, or sequence the human genome. An effort to set research goals for genetic engineering that supports the transition to agricultural sustainability could provide a model process for sustainability science and lead to productive intersections of separate fields of scientific endeavor.
- **The international development community should also support an agenda for the future development of GE crops that considers the risks, benefits, and context for developing countries.** The planning framework and conceptual approach outlined in this paper focus on U.S. domestic agriculture. Developing countries, however, are home to much of the world's biodiversity and to almost all of the world's hunger, preventable disease, and poverty. Enhancing the design characteristics of GE crops to optimize safety and sustainability could make these crops more appropriate for use in tropical and sub-tropical developing regions, including areas of high biodiversity value and the centers of origin for domesticated plants. Given developing countries' limited resources for development and science, the approach described here may also be a model and framework for establishing scientific and capacity-building priorities in these countries.

The aligned interests of the many stakeholder groups—including farmers, agricultural biotechnology companies and other private-sector interests, federal and state regulatory agencies and research agencies, the scientific community, and nongovernmental organizations—can forge political support to provide answers to the question of how genetic engineering fits into the long-term goals for U.S. agricultural sustainability. A sustainability- based plan for crop improvement has the potential to guide scientific discovery, stimulate product innovation, and inform policy formulation and more constructive public debate to ensure that the crops of the future will safely, effectively, and sustainability serve humanity and the U.S. economy. To create such a plan and to achieve these ends, the following actions are recommended:

- **An independent analysis and futures planning process to better inform decisions about how to apply genetic engineering to the future agricultural systems of the United States.** This process must be created by a partnership of private, state, and federal organizations that focuses upon scientific research and policy for agriculture and plant genetics and that involves other stakeholders in agriculture as well as nongovernmental organizations.

- **A quantitative risk-benefit assessment of the potential impacts of safety traits and sustainability traits achieved through modern crop breeding and genetic engineering approaches and deployed in different cultivation conditions and under different policy and market conditions.** The analysis must also consider the impact of high-value output traits for food, feed, and chemicals upon the commodity-handling system and farm economics as well as theoretical and experimental study of the impact of environmental stress tolerance traits upon plant fitness, ecological competition, and agricultural markets. Ultimately emerging from such a process of multi-stakeholder, multi-expert analysis and planning will be a technology roadmap that promotes coordinated research activities and leveraging of R&D investments in genetic engineering for agricultural sustainability.

- **Increased federal financing to support public goods research for agricultural biotechnology that would not otherwise be undertaken by private corporations.** The first priority should be development of design-for-safety traits to enable subsequent investment in traits that impact agricultural environmental sustainability and human health. Public-private consortia may be appropriate to invest in technologies that are long-term, economically risky, or lack large markets, but are in the long-term interests of the agricultural system.

Agriculture and Sustainability

INTRODUCTION

Amidst the current controversies and polarized debates surrounding genetically engineered crops, few have asked: How does genetic engineering fit into long-term goals for U.S. agriculture? This paper explores the intersection of two critical but rarely juxtaposed science and policy issues: the future of genetically engineered (GE)[1] crops and the path to U.S. agricultural sustainability. Genetic engineering of crops can address some aspects of agricultural sustainability, but its development is currently encumbered by technological issues of efficacy and safety as well as public opposition. As the problems of unsustainable agriculture become more acute, it is imperative to target policy and the billions of dollars of public and private investment in the development of GE crops toward goals such as soil conservation, safe water, habitat protection, healthy food, and profitable farms.

The private and public sectors lack a policy and research plan that addresses the present challenges and future goals of both agriculture and genetic engineering. This white paper describes how the approaches of sustainability and product design can provide a framework to guide national planning and decision-making to benefit U.S. agriculture. The design of future GE crops is explored in the case of the Midwestern United States, where commodity agriculture is facing critical environmental, social, and economic challenges. In this region in 2003, farmers planted about 82 million acres in GE crops, amounting to 41 percent of all the Midwestern acreage planted in the principal row crops (USDA NASS 2004a). This white paper frames an assessment of today's GE crops and planning for the future in terms of the benefits and risks to the (1) environmental, (2) economic, and (3) social sustainability of agriculture. Designing GE crops for safety and sustainability may reduce the risks and increase the benefits of tomorrow's GE crops. Government, industry, the scientific community, and civil society have common interests in improving GE crops for sustainability. There is a need for specific research and development goals and a policy context that reward and enable agricultural sustainability, innovation in genetic engineering design, and ecology-based alternatives to destructive agricultural methods.

TODAY'S U.S. COMMODITY AGRICULTURE IS NOT SUSTAINABLE

Sustainable agriculture refers to agriculture that provides food, fiber, and materials without degrading the capacity of the natural system to provide for societal needs and while providing stable livelihoods for farmers. There are many variations of this definition, but virtually all of them feature a holistic view that emphasizes long-term interests (e.g., preserving natural resource capacity) and integrates goals for environmental protection, economic growth, and social development. In agriculture's sustainable state, soil replenishment matches erosion, nutrient inputs match crop uptake and environmental assimilation, aquatic ecosystems are stable and productive, genetic resources are conserved, pests are specifically controlled, synthetic chemicals are at harmless levels in the environment, and agricultural markets and livelihoods are stable (Dower et al. 1997). Most definitions of sustainable agriculture also acknowledge some acceptable levels of habitat change to meet human needs (Horrigan et al. 2002).

The author does not presume to know what form a sustainable agricultural system in the United States will take or what the transitional pathway to that state will be. Agriculture is likely to always be a mosaic of approaches to productivity and resource conservation—each appropriate to different scales and to different values within the agricultural system, including spiritual, cultural, and political identities. However, it is clear that the transition toward sustainable agriculture must maximize the desired outputs of agriculture—such as human and animal nutrition, soil fertility, clean water, farm income, human health, and landscape aesthetic—and minimize negative impacts of agriculture , including eroded soil sediments, nutrient runoff, pesticide pollution, habitat loss, depletion of nonrenewable water sources, farm failures, and social disruptions. Improvements in plant genetics (either through conventional breeding or genetic engineering) and agricultural practices that reduce negative impacts, increase positives outputs, or do both (as compared to conventional agriculture) are regarded here as more sustainable. Of course, the agricultural system is a complex function of technology, cultivation practice, demand, and policy; production technologies will only play a small part in meeting sustainability goals, and genetic engineering is only one of many tools to improve production practices and improve plant genetics.

Environmental Sustainability

This white paper focuses on the twelve Midwestern states (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin), which produce an extraordinary volume of major agricultural commodities for domestic and international consumption. Together these states account for 87 percent of corn, 82 percent of soy, and 58 percent of wheat production in the United States by volume (USDA NASS 2004b). Though the Midwest contains about 40 percent of the country's total farm area, it accounted for approximately 60 percent of all the harvested area of the major row crops in the last 3 years (USDA NASS 2004a; 2004c). This exceptional level of agricultural production comes at a high cost to the natural and cultivated landscapes and to farmers because of unsustainable agricultural practices and distorted markets.

On the whole, the environmental problems associated with agriculture in the Midwest are not immediately threatening to on-farm production. The availability of low-cost energy and investments in chemical inputs and irrigation systems allow farmers to offset the declining natural productivity and natural resources of the region. Farmers have learned to cultivate land and increase productivity per acre while protecting the immediate resource base, and conservation policy has taken highly erosion-prone land out of production (Paarlberg 2001; Heinz 2002). However, environmental degradation, habitat loss, the cumulative release of chemicals and nutrients, freshwater depletion, and energy consumption create an imperative to replace present production practices with sustainable alternatives.

Modern commodity production and its high use of irrigation and of input chemicals—including pesticides, herbicides, and fertilizers—degrade the environment, thereby imposing a significant economic burden on current and future generations. The intensive agricultural activity of the Midwest occurs in and around the headwaters of the Mississippi-Missouri-Ohio River watersheds, but the resulting pollution drains into the Mississippi River and Gulf of Mexico, creating environmental damage far from the cultivated fields. Agriculture is the largest generator of nonpoint-source water pollution in the United States. Nutrients and sedimentation from agricultural fields are the largest source of impairments in U.S. rivers and lakes. The General Accounting Office estimates that federal agencies currently spend about $3 billion directly on programs to control nonpoint-source pollution. The Environmental Protection Agency has estimated that comprehensively controlling nonpoint-source pollution would cost about $9.4 billion per year (GAO 1999).

Most commodity farming in the United States relies on high levels of synthetic inputs, low- or medium-precision application of those inputs, and only modest use of crop rotations and conservation tillage (ERS/USDA and ERS 2003). Most of the agricultural chemicals in the United States are applied in the Mississippi River Basin, which drains about 7 million metric tons of nitrogen in fertilizer (Goolsby and Battaglin 2000; ERS/USDA and ERS 2003). Applied fertilizer, released soil nitrogen, and manure contribute about 65 percent of the nutrient load in the Mississippi. Excess nutrients (such as nitrogen and phosphorous) that run off farmland lead to algae blooms, eutrophication, harm to aquatic biodiversity, and nitrate accumulation in groundwater. Half of all human-fixed nitrogen, approximately 80 million metric tons, enters the environment via synthetic fertilizer and contributes to greenhouse gas accumulation, air pollution, water contamination, acid deposition, eutrophication, and loss of ecosystem function

(Socolow 1999; Tilman et al. 2002). The highest levels of nitrates and pesticides in U.S. waterways are found in agricultural areas of the Midwest (Heinz 2002).

Agricultural practices also increase greenhouse gas concentrations by adding carbon dioxide, methane, and nitrogen oxides to the atmosphere. In 2001, about 7 percent of U.S. greenhouse gas emissions were from direct agricultural activities (EPA 2003). In addition, traditional tillage that removes plant cover from soil contributes to water, wind, and mechanical erosion that reduces soil fertility and increases sediment pollution. Irrigation may increase levels of salt and dissolved minerals in soils as well as surface waters, and water quality degradation can lead to downstream threats to human health, increased water treatment costs, damage to fisheries, and damage to water systems and infrastructure. Pesticide use releases toxic substances into the environment, harms non-target organisms, accumulates toxins in soil and water, and may create pest resistance to pesticides.

Economic and Social Sustainability

Currently, agricultural production in the United States is carried out at or near economic loss. Present levels of surplus production and farm income are maintained through very large government subsidies designed to secure inexpensive food supplies, protect powerful economic interests, expand agricultural exports, and serve the political interests of the farm states. In addition to direct payments to farmers, other subsidies help support financing, tax breaks, trade protection, energy, irrigation, river transport, and the trade infrastructure that supports agriculture. Estimated funding for agriculture in 2003 under the current U.S. Farm Bill (Farm Security and Rural Investment Act of 2002) is $8.4 billion, which includes $7.4 billion for commodity programs, trade promotion, and rural development (CBO 2002).

Environmentally degrading agricultural practices and declining farm profitability stem from our national policy to reduce commodity prices through subsidies and high production. Commodity farmers have been caught in a price squeeze for the last half century. Over this period, the ratio of the Index of Prices Received for the harvest to the Index of Prices Paid for farm inputs in the United States has fallen from 1:1 to below 1:2 (USDA NASS 1997). New technologies have generally brought the American farmer both higher productivity and lower prices. With no control over prices, farmers have two primary strategies for maintaining and increasing profits: increase yields or lower costs. The pressure on farmers for cost reduction leads to expansion of operations and acreage to cover fixed costs and pressure to select the lowest-cost production solutions. Farmers also can increase yields while reducing the agronomic risk of production and product variability through the use of insect and pest control, irrigation, and fertilizer use. A third approach to increasing profitability is to cultivate crops that have differentiating properties, that is, crops that de-commodify the harvest and raise the price received by the farmer. Small farms and rural communities are declining in numbers and wealth. The U.S. farm economy has been weak for decades: low profitability, hard labor, and more attractive jobs in other sectors and in urban areas have contributed to a migration from agricultural occupations and communities. Since 1935, the total number of farms has decreased by 75 percent, while the average acreage per farm has tripled (USDA 1997 Census of Agriculture).

The Introduction of GE Crops

The first GE crops were introduced in 1996 with the attractive proposition to commodity farmers of environmentally friendly crops, lower input costs, higher revenues, less use of toxic chemicals, less intensive weed and pest management, and the promise that the next generation of GE crops would increase crop prices with new grain qualities (see Table 1). GE crops grew faster in acreage than any other technology in U.S. agricultural history. The first commercial GE crops were based on the bacterial Bt genes (*Cry* delta-endotoxins) for insect resistance and the EPSP (5-enolpyruvylshikimate-3-phosphate) synthase and PAT (phosphinothricin acetyltransferase) genes for tolerance of the glyphosate (Roundup®) and glufosinate (Liberty®) herbicides.[2] The next wave of GE crops is about 5 years away (Syngenta 2002; Arnold 2003; Fraley 2003). Overall, commercial GE crops in the United States have led to measurable reductions in toxic herbicide use, pesticide use, and soil loss in certain crops. Farmer preference for these crops is due to the benefits of reduced labor, easier crop management, increased time for earning off-farm income, and reduced handling of toxic chemicals (Shoemaker 2001; Carpenter et al. 2002; Fernandez-Cornejo 2003; Persley 2003).

GE Crops Welcomed by Large-Scale Commercial Farmers

U.S. farmers show a strong preference for GE crops in some of the most valuable commodity crops; by 2004, 45 percent of the corn crop, 76 percent of the upland cotton crop, and 85 percent of the soy crop were planted in GE varieties (USDA NASS 2004a). Crops engineered through the introduction of transgenic herbicide-tolerant and insect-resistant traits are now planted on over 167 million hectares of soybeans, corn, cotton, and canola in the United States, Canada, Argentina, and China (James 2003). In commercial applications, genetic engineering has been applied to just a few species of the major commodity crops, but thousands of traits of interest to farmers have been genetically engineered in hundreds of species in the lab and tested in field trials; 672 trials in 36 species were approved by USDA's Animal and Plant Health Inspection Service (APHIS) in the first 6 months of 2004 alone (ISB 2004).

While creating benefits for some U.S. farmers, the rapid spread of commercial transgenic varieties has caused disruptions in global commodity trade, changed agro-chemical markets, influenced agricultural practice, catalyzed fierce public protest, and necessitated the creation of novel regulatory laws and agencies for biotechnology oversight. The extraordinary pace of technical innovation and the pace of farmer adoption of GE crops has put policy-makers in a reactive mode—often one step behind new technologies and the discovery of associated hazards. The contentious debate about biotechnology's role in agriculture takes time and energy for institutions that might otherwise apply a more forward-looking and long-term approach to pressing agricultural problems.

The birthplace and center of the global tempest over GE crops is the Midwestern United States—home of the world's first commercial GE crops, the area of highest adoption, and home to much of the proprietary technology for crop biotechnology, resident within the portfolios of Monsanto Company (St. Louis, MO) and Pioneer Hi-Bred International, Inc. (a DuPont Company, Des Moines, IA). Not only is the United States one of the world's major exporters of food, feed, and other agricultural products, but it is also a major exporter of agricultural technology and methods. Almost all of the GE crops planted in the world are based on the technologies, genes, and crops developed in the Midwest. Approximately 90 percent of the GE crop area worldwide is planted in varieties owned by Monsanto that contain insect resistance (Bt expression) and glyphosate tolerance traits (Fraley 2003).

Two Traits and Three Crops

About 99 percent of U.S. and global acreage in GE crops is planted in varieties of corn, soybeans, cotton, and canola that express transgenic traits (a heritable attribute from the introduced foreign DNA) for herbicide tolerance, insect resistance, or a combination of these traits. Herbicide-tolerant corn varieties have been made with transgenes from bacteria as well as corn's own modified and then reinserted EPSPS gene. Insect-resistant corn varieties express the Bt toxins *Cry1Ab* or *Cry1F* to control European corn borer, Southwestern corn borer, corn earworm, and other pests. Herbicide-tolerant corn has been substituted for less than 13 percent of the U.S. corn crop in 2004 due to alternative weed management programs, questions about yield, and acceptance in world markets, whereas about 27 percent was planted in insect-resistant varieties, and 5 percent in the two combined, or stacked, traits (USDA NAAS 2004a). The herbicide-tolerant (glyphosate-tolerant) soybean containing an EPSPS gene from the soil bacterium

Agrobacterium is planted on 123 million acres and accounts for 73 percent of the global acreage of transgenic crops (James 2003). Its adoption has been extraordinarily rapid, with over 1,000 varieties of glyphosate-tolerant varieties now available to farmers. In 2004, an estimated 76 percent of upland cotton was planted in GE varieties, including 16 percent in Bt cotton, 30 percent in glyphosate-resistant cotton, and 30 percent in both traits (USDA NASS 2004a). Canola is a minor crop in the United States, with only 1.5 million planted acres, mostly in North Dakota (90 percent) and Minnesota (5 percent). Introduced in Canada in 1996 and in the United States in 1999, Roundup Ready® canola is now planted on about 80 percent of Canadian canola acreage and one third of U.S. canola acreage. A very small area of U.S. farmland is planted in GE squash and GE papaya varieties that have been genetically engineered for virus resistance.

GE Crops Bring Both Risks and Benefits

SUSTAINABILITY BENEFITS OF CURRENT GE CROPS

Scientific assessments show that the technological approach of transgenic crop improvement has potential benefits in many arenas of agriculture performance, but there are many instances of scientific uncertainty and divergence of scientific opinion (Persley 2003). In assessing how GE crops can facilitate the transition to more sustainable agriculture, our major point of comparison is the benefits and risks of commercial GE crops relative to industrial agricultural practice. From a policy and scientific perspective, GE crops are best compared to all alternative methods in current use (NRC 2000) and ultimately systems incorporating GE crops must be compared to non-GE, non-chemical systems. Assessments of the risks and benefits of GE crops are plagued by controversies over many issues, including data accuracy, alleged bias in industry- or activist-funded studies, adequacy of regulatory testing, questionable grower compliance with regulations, and the sufficiency of scientific knowledge.

Reduction of Toxic Chemical Inputs

A major sustainability goal is to reduce negative environmental and human health impacts by reducing the volume and toxicity of chemicals used in agriculture. Bt crops create direct environmental benefits by reducing the amount of insecticide used to control pests and by reducing the use of highly toxic and non-specific insecticides. Herbicide-tolerant crops create direct environmental benefits by reducing tillage for weed control, by reducing the applications of herbicides, and by substituting glyphosate and glufosinate for more toxic herbicides. Following the introduction of GE crops, use of most major herbicides on soybeans was cut approximately in half, while glyphosate use increased six-fold. Glyphosate is less toxic, less prone to leaching, and easier to manage than herbicides previously used on soybeans. Though year-to-year data vary according to planting and weather conditions, they indicate that expanded use of GE soybeans has reduced the quantity of active ingredient applied per acre, reduced the number of herbicide sprayings, and has supported expansion of conservation tillage (Hin et al. 2001). Traditionally, cotton cultivation has relied heavily on input chemicals, but since the introduction of GE varieties, that have been dramatic reductions in insecticide used for the control of bollworm, tobacco budworm, and pink bollworm. Adoption of GE cotton is motivated by reduced costs, improved pest control, decreased production risk, reduced use of highly toxic insecticides, and improved weed management. With low rates of adoption of herbicide-tolerant corn and lack of alternative chemical treatments for the European corn borer, there have been no notable reductions in insecticide or pesticide chemical use in U.S. corn (Carpenter 2002). In 2002, Monsanto introduced YieldGard Rootworm,® a new corn rootworm product expressing *Cry3Bb*, which may have a greater detectable impact on chemical use, since most insecticide use in corn is to control the complex of rootworm insects that are the most damaging of all corn pests.

Conservation of Soil and Water

Herbicide resistance traits support the use of conservation tillage and no-till practices. Conservation tillage leaves the residue of planted crops on the soil, which reduces erosion, returns nutrients to the soil, retains moisture, sequesters carbon, and provides nutrients and habitat for insects and microbes. Adoption of herbicide-tolerant crops is strongly associated with expansion of conservation tillage, particularly no-till practices, though GE crops are not necessary for conservation tillage (ASA 2001; Carpenter et al. 2002; Fawcett and Towery 2002).

Improvement of Farm Economics

Sustainable livelihoods is a pillar of social sustainability and the input-trait crops can improve farm incomes by either increasing yields or lowering costs. Analysis of data on yields of herbicide-tolerant soybeans is confounded by comparisons of different varieties, commercial vs. experimental conditions, weed management methods, farmer practice and sophistication, year-to-year variance in weather, sample choice, and the lag in incorporation of GE traits into elite varieties. It appears that on average the RoundUp Ready® soybean lines yield a few percent less than conventional varieties, but this lower yield is offset by reduced weed management costs (Carpenter 2001; Carpenter et al. 2002). The farm-level economic effects are also difficult to calculate since they depend upon yield data and must incorporate features of farm financial status and price incentives, volume discounts, rebates, technology fees, and changes in off-farm income. Estimations of the economic benefit of herbicide- tolerant soybeans vary greatly with assumptions about herbicide application rates and the cost and necessity of alternative weed control programs. Studies by analysts independent of industry indicate higher farm-level economic returns achieved primarily through weed control savings, and the U.S. farmer preference for GE soybeans is quite clear (Fernandez- Cornejo and McBride 2000; Carpenter et al. 2002). Estimated economic benefits of Bt corn depend strongly on the level of pest infestation; adoption rates of GE corn are higher in counties with historically high levels of European corn borer. Generally, yields of Bt corn are greater than non-Bt corn when corn borer infestations are low or high, but the economic return (net of the technology fee) is only certain to be positive when infestation is high (Carpenter et al. 2002).

Indirect Sustainability Benefits

Although herbicide tolerance and insect resistance traits have indirect as well as direct impacts on sustainability, most of these indirect benefits (see Table 1) have yet to be measured or quantified and significant information gaps remain. Current GE crops have reduced the volume and changed the composition of insecticides and herbicides used in canola, corn, cotton, and soybeans production. Indirect benefits to the environment that can be deduced from these changes include reduction in energy use associated with manufacture, transport, and spraying of pesticides and herbicides. In theory, toxic chemical inputs to groundwater and surface waterways should also be lower because of reduced chemical use as well as increased use of conservation tillage and no-till practices. Conservation tillage should also increase soil fertility and biodiversity in fields as well as reducing erosion and associated downstream degradation of water quality and navigation of waterways, but this has not yet been convincingly measured. Farmers cite the ease of insect and weed management as the primary reason for adopting GE crops, and presumably this improves the quality of life and farm work and frees time for other income-generating activity. Year-to-year fluctuations in crop plantings, commodity policy, weather and precipitation, insect infestations, crop genetic improvement, and chemical use make it difficult to assess the overall impact of GE crops on agricultural sustainability, though many individual studies show slightly positive trends. It is unlikely that the adoption of GE crops has had a significant impact on key system-level indicators of sustainability, such as changes in total land under cultivation, total energy use, agricultural biodiversity, farm income and income stability, total water consumption, or fertilizer use.

SUSTAINABILITY RISKS OF CURRENT GE CROPS

GE crops raise environmental and health concerns associated with their impacts—direct and indirect—upon human food safety, ecosystem health, animal safety, loss of genetic diversity, and resource depletion (see Table 1). Environmental hazards may be direct, such as a chemical interaction with living things, change in weediness or invasiveness of a crop, and the flow of genes to weeds and wild crop relatives. Indirect impacts on the environment occur through changes to agricultural practice that impact the environment, such as reduced effectiveness of weed and pest control, impacts on biodiversity, and effects on soil and water from changed chemical and cultivation practices (Dale et al. 2002).

Potential Loss of Valuable Agricultural Tools: Glyphosate and Bt

Should insects develop resistance to Bt toxin or weeds develop resistance to glyphosate under the selective pressure of GE crops, then future farmers will lose these tools and may resort to more harmful alternatives. This possibility is of particular concern to organic farmers who do not have chemical alternatives to Bt. Though Bt lacks some resistance-promoting features of other types of insecticides, prior to the advent of GE crops it had never been used on such a large scale or at such high and constant levels. Herbicide resistance develops when a weed population is under strong selective pressure of herbicide use. Herbicide resistance is not unique to biotechnology crops, and resistance to glyphosate has been slow to appear but is likely to emerge with greater use. Approximately 275 cases of herbicide resistance in 165 species of weeds have been documented, including four species with reported resistance to glyphosate. Glyphosate-resistant horseweed (*Conyza canadensis*) in Indiana, Tennessee, and the Mid-Atlantic appeared after the introduction of GE crops (Heap 2003). Consistent, heavy use of glyphosate has caused a shift in weed populations to weeds that are more tolerant of glyphosate. Both weed shift and herbicide tolerance may be managed within croplands by herbicide rotation and conventional weed management, but this limits herbicide choice and increases the burden of weed management.

Risks to Biodiversity

Because conservation of biodiversity, natural habitats, and the Earth's genetic resources is key to providing for future human needs, sustainable agriculture seeks to minimize impacts upon biodiversity. Direct negative impacts of GE crops upon biodiversity might stem from the flow of transgenes and their genetic control elements into the gene pool of other species or non-GE crops, from the toxicity of transgene products to non-target species, and from the creation of weeds. Concerns about impacts upon biodiversity are particularly great in the centers of origin of major crops, all of which lie outside the United States. Export of GE grain and growth of GE crops in those areas merit special caution and research. Indirect effects on biodiversity may also relate to the intended trait function, such as herbicide crop management acting to impact biodiversity in crop fields through reduction of weed habitat and seeds, as shown in farm-scale field trials in the UK in corn, sugar beet, and canola (Firbank 2003).

Preservation of Crop Genetic Diversity

Genetic diversity is a key element of overall biodiversity. The genetic diversity of crops and their close relatives is critical to the continued improvement of crops and the resilience of the system to respond to new biological and non-biological (abiotic) pressures. Studies of U.S. soybean and cotton germplasm after the introduction of GE crops showed no reduction in genetic diversity or crop uniformity (Bowman et al. 2003; Sneller 2003). When a transgene is put into a crop, that transformation event is then bred into hundreds or thousands of varieties (the genetic background) for cultivation and does not limit crop diversity or reduce the value of diverse varieties to plant breeders. Genetic engineering may increase the value of investment in gene banks; transgenesis allows inter-species movement of traits and thereby increases the value of genetic conservation while unknown risks raise the value of conserving non-GE seed stocks.

Gene Flow

Gene flow refers to the movement of genes (in this case engineered genes) from the cultivated GE crop to sexually compatible, non-GE crops, local landraces, or wild species. Gene flow occurs among cultivated crops and among crops and their wild relatives and is one of the mechanisms that generate and maintain crop genetic diversity (Ellstrand 2003). If the transferred gene confers greater fitness, it may become part of the gene pool (introgression) and there may be effects upon the natural population of recipient plants. However, under constant gene flow from cultivated fields, even a trait that confers reduced fitness may have an impact. The consequences of gene flow depend on the transferred gene and the ecology of the recipient species. Soybean is a self-pollinating species with no wild or weedy relatives in the United States; thus, gene transfer is considered highly unlikely. Gene flow is of significant concern in the U.S. corn crop because of possible crossing of GE corn varieties with corn grown under certified organic conditions and because of the chance of gene flow from GE corn planted near landraces and ancestral species in corn's center of origin in Mexico (Alvarez-Buylla 2003). Transgenes have been found in Mexican maize landraces, most likely as a result of the import of U.S. corn.[3] Several wild relatives of cotton are native to Florida and the South. There is great concern about gene flow from canola (oilseed rape), which can hybridize with a range of Brassica species, including weeds and commercially important grasses. The extent of GE canola planting in Canada is so great that gene flow has eliminated the nascent organic-certified canola industry. Many ecological factors affect whether a fitness-enhancing transgene will become established and lead to changes in natural populations. Indications that single genes may have such effects make careful study and regulation a high priority (Snow 2003; NRC 2004; ESA 2004)

Toxicity to Non-Target Species

The Bt endotoxin is specifically toxic for certain moths and butterflies in the order *Lepidoptera* and beetles in *Coleoptera*. There is a range of toxicity and specificity among the *Cry* endotoxins, but within the lepidopterans are both pest species (e.g., the European Corn Borer) and non-target species (e.g., the Monarch Butterfly). After reports of Bt corn pollen toxicity to the Monarch butterfly in laboratory studies, further field studies and risk assessment showed that such risks were negligible due to the levels of Bt expression, Cry protein specificity, Monarch feeding patterns, and the timing of pollen flow and Monarch migration (Losey et al. 1999; Sears et al. 2001; Stanley-Horn et al. 2001). However, the Monarch studies highlight the importance of understanding toxin specificity, differences among transformation events, impacts at different localities, and long-term toxin survival (Scriber 2001). Also of concern are the potential impacts of Bt expression in GE crop roots on the rhizosphere and beneficial soil microbes. Bt may have a long lifetime in the soil, but no significant impacts on soil organisms such as earthworms, nematodes, protozoa, bacteria, and fungi have yet been found. However, experimental GE plants have been shown to affect soil microbes (Saxena and Stotzky 2001; Dale et al. 2002). Small-scale and limited studies indicate higher levels of in-crop biodiversity in studied GE crop fields relative to those receiving conventional chemical sprays (King 2003).

Weediness and Persistence

Weediness is the quality of GE plants to become a weed in cultivated fields and may be related to the persistence, or invasiveness, of a species in a non-crop habitat. There is no evidence yet of weeds or invasive plants resulting from commercial GE crops, though this remains a concern for future traits and species (e.g., drought tolerance in commercial grasses). The characteristics of weediness—such as seed shattering and dispersal—are not features of domesticated crops nor properties conferred on plants by either the glyphosate-tolerance or Bt-expression transgenes. Though it is debated whether a single gene could promote weediness, it is unlikely that crops such as corn, cotton, canola, or soybean that do not have weedy characteristics will become weedy or invasive (Crawley et al. 2001; Crawley 2003; King 2003).

Hazards to Human Health

There are several human food safety concerns associated with genetic engineering, including the possibility that DNA may have some toxic effects, that introduced proteins may be toxic or allergenic, that genes may transfer to gut microflora, or that the potential mutagenic effect of transgenesis will have activated toxic or allergenic genes. Food safety of GE crops and methods for assessing food safety of future crops have been developed in the United States and by the Codex Alimentarius, the joint food safety standards commission of the United Nations Food and Agriculture Organization and the World Health Organization, which all compare GE foods and their closest counterpart for substantial equivalence and then focus on the safety of any intended or unintended differences (EU 1997; FAO/WHO 2000; Kuiper et al. 2001). In the case of the current major GE crops, the EPSPS gene in the glyphosate-tolerant crops is widely present in food and feed from non-GE plants. Extensive toxicity and allergenicity studies have been performed on mammals with the Bt *Cry* gene endotoxins with no adverse effects. Current commercial GE crops have been determined to be safe to eat by numerous scientific reviews using present regulatory requirements (SOT 2002; Persley 2003).

In 2000, investigators from the environmental NGO Friends of the Earth discovered contamination in U.S. foods processed from the StarLink™ Bt feedcorn variety. StarLink expresses a truncated *Cry9C* gene, whose product has some characteristics of a potential allergen, though no suspected toxicity. Allergenicity of *Cry9C* was never proved or disproved, though the Centers for Disease Control found no link between *Cry9C* and reported reactions (CDC 2001). The StarLink™ episode did valuably highlight the importance of allergenicity testing and the inadequacy of voluntary U.S. FDA regulations regarding toxicity testing, data collection and transparency, and the analytic methods for determining equivalence and fueled concerns about the future production of pharmaceutical products in corn (EPA 2000; 2001; Kuiper et al. 2001; Freese 2002; Gurian-Sherman 2003).

Drug Resistance Markers

Drug resistance genes and other markers are included as ancillary elements to the transgene to allow selection for transformation and thus become integrated along with the transgene into the targeted plant genome. The first generation of biotech crops used such markers and, though not expressed, the Roundup Ready® and Bt crops contain markers for either streptomycin, beta-lactamase, neomycin, or hygromycin. Several major, independent reviews concluded that it was not likely that intact antibiotic resistance genes could survive human digestion and then be incorporated into bacteria (FAO/WHO 1996, 2000). However, public concern about the use of antibiotic markers that may have medical importance has prompted the development of alternative methods for selection.

Unexpected Effects of Integration and Recombination

Though current GE crops are tested for stable Mendelian inheritance and the presence of only one to three copies of the transgene, the sites of genomic insertion are not well characterized. There is an important concern that the insertion of the transgene might disrupt, down-regulate, or up-regulate other genes at that locus or activate mutagenic processes or gene expression (pleiotropic effects) in the plant leading to loss of fitness, toxicity, altered metabolite levels, or changed nutritional value. There are also concerns that some DNA sequences used in genetic engineering may be mobile in the genome or lead to higher mutation rates. Experimental expression of transgenes in a variety of crops has revealed unintended effects upon plant metabolism and point to the importance of profiling GE crops at the plant, tissue, DNA, mRNA, protein, and metabolite levels (Kuiper et al. 2001).

Threats to Social Sustainability: Political, Ethical, and Economic Concerns

Civil opposition to current GE crops and genetic engineering in general has developed because of public concerns about the environmental and health hazards mentioned above and because of the agricultural,

TABLE 1. Concerns (–) and Benefits (+) Associated with Current GE Crops by Different Stakeholders

Trait		Environmental	Economic & Social
Transgenic modification in general	DIRECT	+ Increase value of genetic diversity – Threat to biodiversity and to genetic diversity – Human health (food) hazards	+ Accelerated crop improvement + New agronomic traits – Loss of world trade markets – Violation of ethics and personal beliefs
	INDIRECT	+ Biological technologies replace chemical inputs – Support of destructive agricultural and economic systems	+ Increased seed company and farm income – Exacerbation of low commodity prices caused by overproduction – Depression of farm income – Increased corporate control – Need for new regulations
Bt expression	DIRECT	+ Crop pest protection + Lower production risk + Reduced insecticide use – Bt-resistant insects – Toxicity to non-target insects	+ Reduced insect management costs + Increased financial returns during pest infestation – Contamination of organic-certified crops
	INDIRECT	+ Better farmer safety – Gene flow to non-GE crops and landraces	– Loss of organic-certified markets
Glyphosate Tolerance	DIRECT	+ Improved weed management – Herbicide-resistant weeds	+ Reduced weed management costs – Contamination of organic-certified crops
	INDIRECT	+ Expansion of conservation tillage + Improved soil and water retention	+ Reduced labor time in weed control + Increased opportunity for non-farm income

Note: Direct benefits and risks are those associated directly from the introduced trait or modification and indirect benefits and risks are those associated with changes in agricultural practices.

economic, and political system in which GE crops have been developed, marketed, and regulated. Some believe that biotechnology and conventional agriculture are both rooted in a paradigm of reductionism and property ownership that is incompatible with the ecology-based and community-centered paradigm of sustainable agriculture (Beus and Dunlap 1990; Lyson 2002). Genetic engineering is intensely identified with the large farms and input suppliers of the chemical-based production paradigm, making genetic engineering a wedge between conventional farming and alternative approaches. Most social, economic, and political issues and concerns have their origins in:

1. A mistrust of the government institutions that are mandated to protect society against harmful impacts of products and technology;
2. A mistrust of the corporations that develop and own most of the technology and their weak reputation for socially responsible behavior;
3. Lack of accountability, strict liability, and transparency of the public and private institutions responsible for developing, regulating, and promoting the technology;
4. Economic interests in other agricultural approaches, local agricultural systems, or national trade;

5. The potential of new technologies to alter the power within the agricultural value chain and views of what is a fair and desired future for agricultural communities and social equity; and

6. Religious and ethical opposition to humankind's right or wisdom to alter genomes.

These six areas are deeply embedded in personal values and beliefs and concerns may be mitigated by policy interventions. Specific views may vary with a stakeholder's position in the value chain and relative standing in the competition among different social objectives and among different approaches to agricultural productivity.

Respecting Differences: Segregation and Labeling

Three issues relating to social controversies that may be partially addressed through technical approaches such as the improvement of GE crop design are crop segregation, legal liabilities, and regulatory oversight. Concerns about the safety of GE crops and other cultural and political reasons for distinguishing between GE and non-GE crops may be addressed through the segregation and labeling of GE crops. Such segregation is not required in the United States but appears to be a likely future feature of many of the major foreign markets for human food crops, such as markets in nations that have ratified the Cartagena Protocol on Biosafety to the Convention on Biological Diversity and member states of the European Union that now require product labeling and labeling of commodity shipments of food and feed.[4] For the first generation of input trait crops, the potential to cross-pollinate with non-GE crops and to create volunteer plants creates new economic liabilities for farmers that threaten the economic gains of using those crops. In addition, GE crop products may mix with non-GE crops and jeopardize export or use in markets that demand non-GE products. Some producers are likely to deliberately or inadvertently use GE crops without the right to do so, as is the case with traditional proprietary varieties (Smyth et al. 2002) and find themselves under new legal threats.

Though current GE crops have not directly precipitated any significant detectable environment or human health damage in the United States, existing GE crop safety regulations, their interpretation and implementation, their application post-commercialization, and their enforcement appear to be inadequate to safeguard against future harm (NRC 2000; 2002; Gurian-Sherman 2003; Jaffe 2003; Taylor and Tick 2003). The U.S. regulatory system and scientific advisory bodies have concluded that traits—rather than the process of their creation—are the basis for considering risks, yet have also recognized that transgenesis creates unintended effects on plant genetics (NRC 2002). Bill McDonough, a leading designer of environmentally friendly buildings and products, has said that government regulations signal a failure of design and that better designed products would need far less regulation (McDonough and Braungart 1998). Similarly, many of today's biotechnology regulations signal opportunities to improve design. This white paper suggests that the crops of the future may be designed for safety to relieve regulatory demands for refugia management, segregation, and extensive testing and may include specific markers to assist segregation and labeling and to identify actors in the seed distribution chain.

Designing GE Crops for the Future

Genetic engineering and other techniques of modern biotechnology move crop improvement firmly into a new realm of product design that also enables an engineering approach to addressing the concerns and benefits outlined above. The risks and benefits of GE crops are determined by their design; the trait, the trait's intended effect on agriculture or contribution to society, and the unintended consequences of the gene construction and trait. More specifically, the impacts of genetic engineering arise from these five aspects of engineering design:

1. The identity of the genetic modification, and the timing, level, and location of transgene expression;

2. The probability and consequence of the transfer of the genetic modification to a related or unrelated species;

3. The probability and consequence of the GE plant having a different ecological impact than the non-engineered species;

4. The intended effect of the genetic modification and how it may exacerbate or eliminate environmentally harmful agricultural practices; and

5. The human and animal benefits or risks of the GE plant and its products.

Today, the issues that have emerged from GE crop introduction are being addressed by both opponents and proponents of GE crops through strategies at the end of the product pipeline such as regulatory measures, intellectual property rules, growers' agreements, labeling and segregation laws, and compliance tests. While such end-of-pipe measures are the only options for current products, upstream design goals for safety and sustainability can raise the value of future GE crops by inspiring research and innovation, reducing negative health and environmental impacts, increasing the social acceptance of biotechnology, and enhancing their social utility (Daniell 1999; DEFRA 2001).

Two Design Goals: Increase Safety and Increase Long-Term Value

Two upstream design goals are of central importance for research and development of GE crops: *design-for-safety* and *design-for-sustainability*. Design-for-safety addresses social and environmental concerns inherent to genetic engineering that can be approached through improved design (see Table 2). This first goal represents an integral step toward the second goal, design-for-sustainability, which is aimed at increasing the social, environmental, and economic value of GE crops through traits that improve agricultural sustainability (see Table 3). Design-for-safety includes elements that address concerns about gene flow, unintended consequences of genetic modification, non-target effects, and human food safety. Most of the mechanisms for design-for-safety remain to be refined. Designing GE crops for agricultural sustainability seeks to reduce the environmental footprint of agriculture, enhance crop and natural biodiversity, support economic growth, improve the farm economy, improve human health, and provide broad societal benefits. Most of the traits for design-for-sustainability are complex and not yet elucidated.

Design-for-safety is about the technology itself, whereas the higher goal of design-for- sustainability is about *how* the technology is applied to meet human needs. In this white paper, safety is defined as the *public acceptance of risk*. This definition combines the public perception of benefits with the scientific assessment of risk and reflects the complex collision of societal values with scientific data and uncertainty that often characterizes the setting of policy and investment priorities.[5] This definition incorporates what some may dismiss as perceived risks rather than scientifically documented hazards and probabilities. For example, though scientific assessments have determined that the human health risk of ingesting antibiotic marker genes is very low, the public does not find such risk acceptable and considers antibiotic markers *unsafe*. A design-for-safety goal is to eliminate DNA sequences such as antibiotic marker genes that pose risks or might not be perceived as safe. Designing GE crops for safety will, in itself, address some of the issues and concerns associated with genetic engineering and enable GE crops to be designed for agricultural sustainability. Put simply, the technology must be considered safe to ensure that future GE crops will have markets.

Time is Money: Design-for-Safety Lowers Product Development and Regulatory Costs

The tools of modern plant molecular genetics are rapidly increasing the rate at which the genes and mechanisms of complex traits may be identified and understood. High-throughput methods for gene discovery and for proteomic and metabolic profiling, combined with the increasing efficiency of gene conversion by mutagenesis, gene-replacement, and transformation will significantly increase the numbers of transgenic plants and the rate of their development. The ease of creating transgenic plants will increase the demand on regulatory agencies to approve and monitor field trials and raise the overall risk of an adverse consequence of those trials. This demand provides incentives to incorporate environmental con-

TABLE 2. Priorities for Genetic Engineering Design-for-Safety

	PRIORITY				
Design Element	**Environmental Safety**	**Food Safety**	**Regulatory Costs**	**Unintended Risks**	**Crop Segregation**
Control of transgene flow	↑	↔	↘	↓	↗
Control of transgene expression	↑	↗	↘	↓	↔
Control of transgene integration	↗	↗	↘	↘	↔
Genetic use restriction technologies	↑	↔	↔	↓	↗
Removal of non-expressed sequences	↗	↔	↘	↘	↔
Control of fertility	↑	↔	↘	↓	↗
Phenotypic markers	↗	↗	↔	↘	↗
Genetic markers	↔	↔	↔	↘	↗

Note: The symbols used in this table denote the estimated impact of design elements on priority economic, environmental, and social issues as Strong Increase (↑), Moderate Increase (↗), Neutral (↔), Moderate Reduction (↘), or Strong Reduction (↓).

tainment mechanisms within the background genetics of experimental plants and transgene constructs, to address public acceptance as a matter of product design, and to increase knowledge of the ecological impacts of specific traits.

The total costs for the introduction of a new GE crop from initial discovery to marketing approval may exceed $100 million; the time from discovery to marketing approval is close to 7-10 years.[6] This high financial barrier places GE crop development within the reach of only the large multinational agro-chemical and biotechnology companies and leaves little incentive for small- and medium-sized entrepreneurial companies to invest in the field. This high cost also means that to get a return on investment, the target market of any innovation must be very large—such as crops and inputs of industrial monoculture. Discovery and technical innovation that increase the precision and safety of genetic engineering may shorten the development and regulatory time scale. Today, traits that yield only small benefits to farmers, benefits to environmental performance, or traits for minor row, orchard, and vegetable crops are unlikely to attract commercial development. Design-for-safety should lower regulatory costs, accelerate product development, and increase the competitiveness of small companies and public initiatives to develop improved crops (see Table 2).

GE CROP DESIGN FOR SAFETY

Commercial GE crops have demonstrated in the United States that transgenic traits that substitute for chemical production inputs can create economic and environmental benefits for farmers and society as well as new economic, social, and environment hazards. For genetic engineering to be applied widely in the future, there must be both technological and policy solutions to concerns raised by scientists and consumers about the general approach of genetic engineering as well as specific GE crops. The technical objectives of design-for-safety—already significant areas of uncoordinated corporate and public research—are to increase the precision of gene insertion, to limit inserted genes to just the necessary DNA sequences, to control when and where those genes are turned on, and to prevent new genes from moving elsewhere in the genome of target species or into the genomes of related species (see Table 2).

Getting Genes Where You Want Them: Gene Targeting

Homologous recombination (gene targeting) would be as profound a development as the first transgenics and is a much sought-after goal, yet it has only been achieved in a few higher plant species (Oh and May 2001; Hanin and Paszkowski 2003; Hohn and Puchta 2003). If genes could be targeted to a specific place in the genome or targeted to replace an existing gene, present concerns about the mutagenic effects of random gene insertion may be eliminated. Targeted gene insertion and replacement may also reduce uncertainties about unintended impacts of over-expression or unnecessary expression of transgenes. Altering plant characteristics by efficient gene replacement would solve issues of transgene instability, some of the questions of substantial equivalence, and also accelerate understanding of complex traits (Britt and May 2003). Gene targeting is also the means by which genes expressing toxins, allergens, or anti-nutritional compounds might be silenced. As genomics generates a large number of target genes to be replaced, modified, or transferred, it is likely that transgenes or modified sequences will be chosen from varieties in the same species or homologous genes from closely related plant species (Strauss 2003). Once genes can be easily swapped and modified, much genetic engineering would not involve the introduction of foreign genes or sequences and could become indistinguishable from conventionally mutated and bred varieties.

Just the Gene Please: Transformation Methods and Sequences

Both the hazards and public fears of the genetic engineering process may be addressed by eliminating unnecessary gene sequences that create concerns about mobile genetic elements and mutation hotspots. Greater transformation precision in genetic engineering is a goal that could eliminate concerns about unnecessary, undesirable, or unacceptable gene sequences in transgenic plants. Plant transformation (gene insertion) efficiency is so low that specific genes (selectable markers) are needed to select the transformed plants during transgenic plant development. Higher transformation efficiency would lower the costs and duration of product development and allow refinement of plant designs and more extensive testing. Removal of selectable marker genes, particularly antibiotic resistance markers, as well as removal of viral transgene promoters is an improvement of precision and a design solution to a human health and environmental concerns.[7]

Gene Expression When and Where Its Needed: Temporal and Tissue-Specific Control

Technologies for the temporal and tissue-specific control of gene expression may reduce uncertainties about the unintended impacts of over-expression or unnecessary expression of transgenes (Dale et al. 2002). In addition, continuous and ubiquitous gene expression may create yield drag and some traits such as pest resistance and herbicide tolerance may not need to be expressed in edible seeds and fruit. The timing of transgene expression may be achieved by linking the gene of interest to an inducible gene expression system or to promoters that are responsive to specific nutrients, metabolic signals, wound signals, or specific stresses. Over a dozen systems of specific chemical induction have been developed and show promise, yet none have the ideal combination of high expression, specific induction, and low toxicity (Padidam 2003).

KEEPING GENES IN PLACE: ENVIRONMENTAL CONTAINMENT AND CONTROL OF GENE FLOW

Technologies for the environmental containment of transgenic crops and the prevention of transgene flow to non-transgenic crops may significantly reduce concerns about impacts upon biodiversity and non-GE crops. There are new technologies for control of gene flow, but there is still relatively little knowledge of the ecological and agronomic effects of gene flow. Long-term and complex studies are needed to track gene flow, but to date the private sector has been unwilling to support such efforts. The potential risks of gene flow, the benefits of its containment, and the knowledge of fundamental plant processes that may be gained from its study make this a priority for the public and private sectors (Snow 2002).

A variety of strategies could help ensure that transgenic crops do not cross with non- transgenic crops or that seeds of such crosses fail to germinate. These include germination conditional upon application of a chemical inducer, restriction of the transgene to chloroplasts and maternal inheritance, and means for seed lethality. Promoters or repressors may be used to control the expression of transgenes or to limit transgene expression in foundation or progeny lines that are dependent upon a hybrid plant system and would not function under random reproduction (Moore et al. 1998; Schernthaner et al. 2003). Another technology of interest is the transfer of clonal reproduction (apomixis) to non-apomitic plants for the maintenance of high-yielding varieties and control of pollen flow and crossing to wild relatives (Daniell 2002).[8] In addition, traits for the control of flowering, fertility, and reproduction, and varietal and trait genetic use restriction technologies (v-GURT and t-GURT) may be valuable control points for gene flow.

Relieving Separation Anxiety: Segregating Tools

Technologies for identity preservation and segregation of GE crops will facilitate compliance with labeling regulations, support those consumers who choose not to eat or purchase GE crops, and enable distribution channels for high-value crops. Means of preserving crop identity allow for protection of proprietary genetics and for environmental monitoring and may be accomplished by the voluntary or mandatory inclusion of unique identifier sequences (Gressel and Ehrlich 2002). Rapid gene discovery methods may allow the incorporation of distinguishing traits for grain seeds, such as unique colors and shapes, into elite germplasm.

GE CROP DESIGN FOR SUSTAINABILITY

Designing GE crops for sustainability focuses upon reducing the environmental impact of agriculture and increasing its economic and social value (see Table 3). Sustainability traits do not degrade the agricultural or natural environment, discourage use of toxic inputs, retain effectiveness over time, and integrate with other agricultural practices (Hubbell and Welsh 1998).

Resource Productivity and Agronomic Security

Design-for-sustainability aims to increase agricultural productivity, that is, yield as a function of the sustainable land, water, energy, soil, and nutrient resources. There is a considerable body of basic plant research that is directly applicable to problems of environmental sustainability, including research in nutrient utilization, abiotic stress tolerance, pest and disease resistance, yield improvements, and improved crops for livestock production. Most of this research is at a stage that proves in principle the improvement of plant performance through genetic engineering, but the impact of these traits has not been modeled or measured in the field.

Reducing Pollution: Nutrient Utilization Traits

Improvement of nutrient utilization may be a strategy to reduce input costs, the application of fertilizer, and fertilizer's negative environmental impacts. The three key limiting minerals for agricultural productivity are nitrogen, phosphorous, and sulfur. The availability of inexpensive fertilizers and low cost of over-use have meant that mineral utilization has yet to become a primary concern of plant breeders (Hell and Hillebrand 2001). However, the negative impacts of fertilizer run-off, rising costs of energy and greenhouse gases in fertilizer manufacture, and the $9.5 billion farm fertilizer market make mineral utilization traits increasingly attractive targets for genetic improvement (USDA NASS 2003). There is considerable knowledge about the reactions of crops to nutrient supplies and progress is rapid in identifying genes involved in mineral acquisition and allocation. Transgenic over-expression of nitrate and phosphate transporters has increased uptake in experimental plants but has not yet been applied to field crops. Nutrient utilization for yield and nutrient conversion are traits in screens in Monsanto's early product pipeline (Fraley 2003). Another target for genetic manipulation are the exudate enzymes and acids that allow the solubilization and uptake of nutrients via

TABLE 3. Potential Applications of GE Crop Design-for-Sustainability

Application	Description of Traits and Their Potential Benefits
Input Traits	Traits that reduce the need for production inputs, including chemical fertilizers, insecticides, and herbicides. Direct benefits: reduced production costs through traits such as disease resistance, pest damage tolerance, pest resistance, herbicide tolerance, nutrient utilization, and drought tolerance. Indirect benefits: air and water quality, water quantity, land use efficiency, reduced soil loss, farm income, and farmer safety.
Agronomic Traits	Traits that lower production risks, increase yield, or simplify crop management, such as faster growth, early maturation, enhanced photosynthesis, and higher yield. Direct benefits: reduced costs and risks as well as lower finance costs for production. Indirect benefits: creation of opportunities to remove land from production.
Value-Added Traits	Traits that increase the farm-gate value of crops for their attractive processor or consumer characteristics such as higher percentage of high-value ingredients, color change, and flavor change. Includes the traits for health, medical compounds, industrial materials, and energy described below. Direct benefits: higher farm revenues and improved compeitiveness of U.S. farmers in global commodity markets. Indirect benefits: creation of opportunities to remove land from production, improved rural livelihoods, and reduced energy use and pollution by replacing chemical methods for producing high value food ingredients and industrial compounds.
Health Traits	Traits that result in higher percentage content of healthy oils, specific amino acids, protein levels, vitamin content, or improved starch and sugar composition and reduced anti-nutritional compounds. Direct benefits: higher farm revenues and improved competitiveness of U.S. farmers in global commodity markets adn improved nutrition for consumers Indirect benefits: improved rural livelihoods and reduced burden of poor nutrition and disease.
Medical Compounds Production	Traits that enable production of pharmaceuticals, vaccines, and diagnostics in plants. Direct benefits to farmers: creation of much higher-value crops. Indirect benefits: reduced costs, waste generation, and energy consumption in pharmaceutical production and lower healthcare costs
Industrial Materials and Energy Production	Traits to produce or optimize production of industrial materials and chemicals, such as plastics, starch, and ethanol, currently derived from fossil fuel feedstocks. Direct benefits to farmers: higher-value crops, reduction of over-supply of commodities, and reduced dependency upon fossil fuels. Indirect benefits: reduced greenhouse gas emissions, higher levels of carbon sequestration, and reduced U.S. dependency on imported fossil fuels.
Bioremediation of Toxic Compounds	Traits that enable plants to accumulate, sequester, or metabolize toxic compounds. Direct benefits: safer, cheaper, clean-up of toxic sites and soils in industrial areas.

pumps, carriers, and channels into the root cells. Genetic engineering approaches to mineral acquisition and metabolism will require greater understanding of complex pathways (Hirsch and Sussman 1999; Hell and Hillebrand 2001).

Water Conservation and Climate Stress: Abiotic Stress Tolerance Traits

Crop tolerance of stresses such as drought, cold, heat, and salinity (abiotic stress) may allow greater consistency of production, higher yield and quality, greater flexibility in planting locations, and resilience to natural and human-caused climatic variations. Progress in this area suggests that transgenes for these traits may become commercially viable within the decade.[9] Of the abiotic stresses, drought tolerance may be a particularly valuable trait with the potential to reduce irrigation costs, production risks, risks of climate change, and harmful run- off from fields. Monsanto has publicly shown photographs of corn and soybeans apparently transformed with a single gene for drought tolerance discovered in screens in Arabidopsis that confers significant drought tolerance (Monsanto 2003). Transgenic strategies for salt tolerance include the production of proteins that reduce the damage of salt stress or the expression of proteins that help plants maintain homeostasis and there is evidence that salt tolerance may be achieved in a relatively direct manner (Ruiz 2001; Zhu 2001; Apse and Blumwald 2002; Shi et al. 2003). As traits of abiotic stress tolerance, pest or pathogen resistance, or altered propagation are introduced into crops, there may be changes in weediness, invasiveness, or ecological niche. Whereas today's GE crops express genes regardless of environment, plants engineered with complex traits for abiotic stress tolerance may exhibit more complicated interactions with the environment and merit long-term studies for performance in different environments (Strauss 2003).

Securing the Harvest: Disease and Pest Resistance Traits

North American farmers spend $7.8 billion on chemical crop protection, including approximately $3.7 billion for insecticides and fungicides (CropLife 2002). Identification and manipulation of genes for disease resistance, pest resistance, and tolerance of pest damage may improve quality and quantity of harvested yields, reduce pesticide and fungicide use, and lower farmworker exposure to chemicals (Welsh 2002). The development of plants with both specific and general pest resistance may greatly reduce the use of broad spectrum insecticides and the use of insecticides against insect disease vectors. The result may be a more natural balance of pests and predators in agricultural fields and crop margins and higher levels of agro-biodiversity in fields with genetic engineering strategies for pest control compared to those with chemical control methods (NRC 2000). A wider range of genetic strategies for pest resistance is also desirable to reduce the selective pressure that is present in fields with Bt crops. Experiments have investigated a wide variety of transgenic insecticidal toxins, including proteinase inhibitors, lectins, and chitinases. In the longer term, genetic engineering may allow the enhancement of bio-control strategies and molecular biology tools may accelerate understanding of bio-control agents found to control pests (Gerhardson 2002).

Increasing Production Reliability: Yield Traits

Most of modern crop breeding aims to improve the yield and stress resistance of varieties optimized to grow in different soil and climate conditions. Agricultural inputs also serve to increase the yields and reduce the variability of production. Plant research is increasing our understanding of basic plant metabolism and the genes that partition metabolites and energy among different plant tissues such as between stems and seeds. Genes may also be identified that increase basic photosynthetic efficiency. Increasing post-harvest stability and post- harvest pest resistance could increase effective harvest yields and also create benefits throughout the commodity-processing and food distribution chain. Increased yield, however, will not result in removal of land from production absent appropriate land use policy.

Reduction of Livestock's Harmful Impacts: Feed Nutrition Traits

Development of traits to improve the effectiveness of corn and soybean as animal feeds via specific protein and oil levels may create higher-value feed crops and reduce land under cultivation. Higher-nutrition feeds with greater conversion efficiency (digestibility into meat and milk) will reduce total demand for animal feed as well as lowering waste production. Pigs and chickens cannot digest phytic acid, the principal form of phosphate storage in feed grains (and possibly a major anti-nutritional factor in animals and humans), which contributes to the significant phosphorous pollution in their wastes. Transgenic strategies for

Box 1.

The Smarter Corn Concept Crop: A Hypothetical Case of Applying Design-for-Safety and Design-for-Sustainability Goals to Stimulate Research and Innovation

Technical Improvements: This imaginary hybrid corn expresses a Bt toxin modified for greater specificity for the target pest with tissue-specific expression in the primary tissues of insect attack. The transgene is not expressed in pollen; it may be induced upon pest attack by linkage to stress-responsive promoters. Targeted gene replacement allows bi-annual rotations of Bt toxins to reduce the likelihood of resistance development. The same imaginary variety also resists rootworm via a specific Bt toxin under temporal and spatial control in roots only during the early part of plant growth when plants are at risk. A genetic use restriction technology (GURT) maintains seed fertility, but not the transgene upon reproduction, making the trait specific to the planted (and purchased) generation of crop. Marker-assisted breeding has been used to introgress enhanced nutrient and mineral assimilation traits that were identified by high-throughput methods, as well as drought tolerance. Variety-specific marker sequences designed for low-cost tests help ensure segregation and identity preservation. When the same variety is used for chemical production, additional traits of sterility, seed lethality, and phenotypes such as kernel shape or color are added for additional levels of containment and ease of segregation.

Risks Mitigated: This hypothetical design reduces real or perceived risks to human food safety, cross-pollination with organic-certified crops, development of resistance to Bt, compliance with refugia regulations, restrictions on seed saving, and impacts on non-target insects.

Benefits Enhanced: The smarter corn results in improved pest protection, reduced use of insecticides, simpler requirements for crop management, lower costs of production, reduced energy use in fertilizers, reduced water use and soil loss, creation of value-added products, and simpler growers' agreements.

reduced phytate or increased phytase levels in animals or their feeds may improve nutrition and reduce the negative environmental impacts of animal wastes (Brinch-Pedersen et al. 2002). Other efforts to improve livestock feeds focus on protein quality (levels of the amino acids lysine and methionine), digestible oils, digestible fiber and starch, and reduction of anti-nutritionals (Cockburn and Phipps 2003).

GE Crop Design for Crop Value: Output Traits

The most significant potential impact of genetic engineering on the agricultural system might be to shift major crop production from commodities to differentiated, high-value products. Genetic engineering holds considerable promise for improving the output traits of crops, including specialty traits for improved storage, processing, animal feed value, production of specialty chemicals, and for human nutrition and food safety. The first generation of GE crops delivered no direct benefits to the retail food consumer; if it had, such benefits might have led to greater public tolerance of risks and fewer consumer fears associated with GE crops. These output trait crops may increase farm income and increase farmers' freedom to choose among crops and niches in the value chain. As the diversity and value of such products increase, greater capacity for identity preservation and segregation through the grain-handling system will be desired and profitable. Output traits may change the balance of perceived personal risks and personal benefits of GE crops for the consumer.

Another new horizon for agriculture is the production of high-value specialty chemicals and pharmaceuticals. These could significantly benefit the environment by replacing fossil-fuel feedstocks currently used to manufacture chemicals and pharmaceuticals with crop-based alternatives. However, these applications of genetic engineering to non-food or feed uses of plants raise new concerns about the security of segregation systems and the emergence of new hazards, thus creating a strong impetus for the design-for-safety measures described above (Freese 2002; Pew and Biotechnology 2002b; Fischer and Commandeur 2003). The high value of crops such as pharmaceutical crops will require strict testing and segregation, yet also create the economic incentives for the development of such systems (Shoemaker 2001). Some portion of the created value will be captured by farmers who themselves may develop relative competitive advantages and expertise for the production, yield, and segregation of certain new crops. Increasing crop value may lead to more coordination within the value chain, new relationships with farmers as contract growers, and fewer participants in the value chain. The ultimate impact on farmers of increasing crop value is not clear, and policy may need to be developed to ensure favorable conditions for farmers.

Enhanced Food Nutrition, Safety, and Consumer Appeal

Genetic engineering of crops to enhance their nutritional profile, safety, appearance, flavor, texture, or other characteristics may be valued directly by consumers. Increasing the vitamin and provitamin content of grains and fruits may increase their value to consumers. Vitamin levels have been elevated with a single transgene in tomatoes, canola, and other crops and it may be possible to genetically engineer the synthesis of most vitamins in plants (Shewmaker et al. 1999; Romer et al. 2000; Zimmermann and Hurrell 2002). Transgenic approaches have been used to increase levels in foods of antioxidants, mineral levels and their availability, and fatty acids (Tucker 2003). Such crops may bring higher prices to farmers, perceived benefits to consumers, and the means to deliver improved nutrition. The multi-billion dollar U.S. consumer market for foods that make health claims (functional foods and nutraceuticals) may make nutrition-enhanced GE crops an attractive opportunity for U.S. farmers, though such crops fall into a complex regulatory context depending on their marketing as fresh food, extracts, or medicines and may have uncertain social value (Kleter et al. 2001; Verrips et al. 2001).

Modifying plant oils has applications for more nutritious human food and animal feeds and for industrial purposes such as the production of oilseeds high in polyunsaturated omega-3 fatty acids and oleic oil. Novel fatty acids produced in plants may have industrial uses as lubricants and drying oils or as precursors to polymers and other materials. Arabidopsis, canola, and corn have all been engineered to create industrially useful fatty acids, though production levels and purity have not yet made these practical, and more research is needed in fatty acid metabolism (Jaworski and Cahoon 2003). Food safety developments may include post-harvest stability that reduces spoilage, elimination of known allergens, and reduced levels of toxins. Other possibilities include reduced caffeine levels in coffee. Changes such as these to modify the levels and composition of proteins, oils, carbohydrates, and secondary metabolites in plants are more complex than the transgenic traits in current GE crops and raise new challenges for testing and regulations (King 2003).

GE Crop Design for Agro-Biodiversity

As one of the tools for plant improvement, genetic engineering may allow a more diverse and specific set of biological controls for pests and pathogens, permit rapid genetic improvement of a wide variety of crops, and support a more diverse agricultural system. It is also important to note that experiments with GE plants have shown complex effects upon trophic levels higher than the immediate target of pest-resistant plants, and much remains to be understood about population impacts upon pests and their predators and parasites. There is an experimental and theoretical argument for GE crop preference to conventional chemical systems, but no one has conducted a direct comparison to integrated pest management approaches (King 2003; Persley 2003). Organic agriculture, conventional plant genetic improvement, and genetic engineering are all based on a belief that biological systems can serve human needs with reduced environmental cost. Future GE crops may help to create convergence among different agricultural systems toward a renewable resource and biology-based agriculture. As plant genetics displaces chemical and mechanical production inputs, the fields of the future may contain more diverse mixes of crops and beneficial plants that increase habitats relative to today's agricultural ecosystems.

GE Crop Design for Bioremediation

Genetic engineering may also help optimize plants for food production on marginal soils, the clean-up of toxic substances and for clean-up of contaminated

TABLE 4. Priority Traits and Technical Developments for Design-for-Sustainability

Sustainability Goal	Traits and Developments	Impacts
ENVIRONMENT		
Clean water and healthy aquatic ecosystems	Nitrogen, phosphorous, sulfur utilization Nitrogen fixation	Reduced fertilizer use and nutrient pollution, reduced energy consumption. Increased soil fertility and reduced fertilizer use.
	Drought tolerance	Water savings in irrigation, less run-off and less leaching of agrochemicals into waterways. Yield stabilization, reduced production risks.
	Disease and pest control	Reduced use of pesticides and insecticides.
Soil conservation	Herbicide tolerance Perennial crops	Expansion of conservation tillage and no-till practices. Long-term development of perennial crops and cover crops to reduce soil loss and tillage.
Healthy climate	Disease and pest resistance Soil conservation Bio-fuel processor traits	Reduction of fossil fuel inputs to agriculture in chemical production and applications. Greater carbon storage in soils. Production of bio-fuels and specialty chemicals in plants.
Biological and genetic diversity	Transgene containment	Protection of natural and crop species and genetic diversity. Reduced chance of weediness, invasiveness, and population shifts.
	Engineering precision and gene stability technologies	Lower costs and risks of crop improvement to facilitate greater agro-biodiversity and crop diversity.
	All input traits that eliminate chemical and mechanical input	Allow greater crop diversity and inter-cropping of row crops and cover crops. Increase in-field diversity and numbers of species of microbes and insects as well as birds and other wildlife.
ECONOMY		
Economic growth	High-value oils, materials, chemicals, and pharmaceuticals	Differentiation of commodity crops into high-value crops with output, processor, and consumer traits. Greater crop diversity and agro-biodiversity.
Low food prices	Risk reduction	Diversity of crops to hedge against market fluctuations. Stabilization and smoothing of production via traits for enhanced pest resistance, disease resistance, and tolerance of abiotic stresses
SOCIETY		
Human health	High protein crops Improved animal feeds Disease and pest resistance	High-protein crops and diverse crops for replacement of meat in diets. Leaner livestock reared without input chemicals. Elimination of pesticide residues in food and water.
	Non-allergenic foods Higher nutritional content High yield	Reduction of anti-nutritional components and allergens. "Nutraceutical" enhancements such as canola and soy low in saturated fats, beta-carotene enhanced canola, increased vitamin and iron content, and improved flavor. Healthier, leaner livestock. Abundant, low-cost food.
Respect of societal views Individual choice	Gene replacement Markers for segregation and IP Phenotypes for segregation and IP	Plants that do not contain genes from other species. Traits that allow for easy segregation and identify preservation to respect labeling laws and individual choice.
Safety: Social acceptance of risk	Environmental and human health safety traits	Lower regulatory costs, regulatory hurdles, and societal opposition Promotion of public-sector technology development Less dominance by large multinational companies.

soils at industrial sites. Plants produce an extraordinary array of secondary metabolites that deter animals, insects, and competing plants, and that also act to increase microbial activity in soils and their bioremediation of soil chemicals (Singer et al. 2003). Plants may be engineered to extract and sequester toxins—including elemental pollutants such as cadmium, arsenic, lead, mercury and organic pollutants such as polychlorinated biphenyls (PCBs), aromatic hydrocarbons (PAHs), and halogenated hydrocarbons—from the soil or to bio-convert toxins to less harmful forms (Zhu et al. 1999; Bizily et al. 2000; Meagher 2000; Bennett et al. 2003; Ruiz et al. 2003). There are only a handful of reports of bioremediation assisted by transgenic crops; this remains an area distant from field application.

Can Technology Address the Social, Political, and Economic Controversies?

The themes underlying the opposition to crop biotechnology merit consideration by both biotechnologists and policy-makers: individual choice, product safety, social value, sharing of public goods technology, transparency, and ethics. These themes may be partially addressed by research, new technology, and policy as well as through transparent and participatory processes to establish priorities. Genetic engineering as part of the transition toward sustainable agriculture is unlikely to be acceptable to the ardent opponents of crop genetic engineering. Opponents believe that proprietary technology is a corporate tool for increased control of farmers and the restriction of individual choice, that genetic engineering entails too many risks and unknowns to be safe, or that it is ethically or morally wrong to create transgenic organisms. It would be naïve to think that further technical refinement could placate the most vehement opposition. However, opinion surveys of the American public suggest that although almost two thirds of respondents are likely to be critical of GE crops, they are also willing to consider the specific benefits and risks of each case and would judge favorably any measures to improve social value (Priest 2000; NSB 2002; Pew and Biotechnology 2002a). Technical innovation to address important economic needs and the environmental and health risks associated with genetic engineering may significantly alleviate, though not eliminate, some of the social, political, and economic controversies of current commercial GE crops.

Aligning Interests and Closing Gaps

BARRIERS TO IMPROVED GE CROP DESIGN

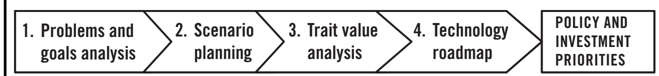
There are high political barriers to developing an R&D agenda and policy environment that will increase the safety and sustainability contributions of GE crops. Powerful agricultural interests are reluctant to acknowledge the unsustainable aspects of Midwestern agriculture, particularly the impacts of subsidies, over-production, and chemical inputs. Admitting risks or the validity of public concerns regarding GE crops may be seen to undermine the U.S. position in the high-stakes international trade disputes over GE crops. A minority of the U.S. public is vehemently opposed to genetic engineering of crops in any form and rejects the notion that GE crops can coexist with other approaches to agricultural production. The industrial, farm, and trade interests that promote GE crops frequently take an “all biotechnology is good” approach and resist asking how it might be better, in part because they do not want to appear to be giving ground to activists. Thus, those driving the extremes of the debate are seldom interested in a moderate and middle-ground view that, like all technologies, genetic engineering and its applications entail both real benefits and real dangers.

Political support for research and development of technologies for environmental containment, improved management of resistance, and safety will require the biotechnology industry to recognize these as issues of public concern or as measurable hazards. The leading agricultural biotechnology companies remain part of the agro-chemical industry and are thus reluctant to directly address the risks of chemically intensive agriculture. Since GE crops are deemed safe by the same regulatory agencies that also set safe limits for pesticides and herbicides, it is difficult and potentially embarrassing to make a case that GE crops are a safer alternative to similarly regulated chemical inputs. The intellectual property environment in the United States is designed for the appropriation of publicly developed technologies by private commercial interests and may not favor investment in technologies for public needs for which there are not yet markets. The Patent and Trademark Law Amendments Act, more commonly known as the Bayh-Dole Act, makes even research performed within federal institutions likely to be licensed by the private sector and thus made inaccessible as public goods in the absence of measures to ensure the public use of agricultural research (Beachy 2003; Atkinson et al. 2003). Though these barriers may create some pessimism as to the likelihood of reform and redirection of agricultural research, there are also powerful interests that may motivate actors in the public and private sectors to partner in pursuit of sustainable agriculture goals. A better coordinated national R&D policy for agriculture and genetic engineering is needed—one that is guided by goals of agricultural sustainability and a vision that diverse sectors of society can align behind.

NEEDED: A FUTURE VISION AND A TECHNOLOGY DEVELOPMENT PLAN

A future R&D agenda for genetic engineering must reflect what society most needs agriculture to accomplish. The R&D areas that may impact agricultural sustainability must be tested through a participatory process involving key stakeholders if there is to be a compelling political, social, and economic case that influences both public and corporate policy. An analytic process should be undertaken to produce a clear R&D agenda, the science policy to support that agenda, and a broad policy agenda to ensure market development, incentives for innovation, and social value. To build support for implementation of the resulting recommendations, the process must include multi-stakeholder and multi-expert research, analysis, and planning.[10] Four elements of the proposed process are: (1) problems and goals analysis, (2) scenario planning of U.S. agricultural futures, (3) trait value analysis, and (4) a technology roadmap.

Figure: A Participatory, Multi-Stakeholder, and Multi-Expert Process for Setting Goals



Goals Analysis and Scenario Planning

The qualitative review in this white paper can provide a starting point to plan a quantitative and comprehensive analysis that includes specific targets and indicators of agricultural sustainability. Scenario analysis is a tool for decision-making under conditions of uncertainty that could employ a multi-expert process to identify trends and uncertainties to develop detailed narratives of multiple plausible futures for U.S. agriculture and the role of GE crops (e.g., Hubbell and Welsh 1998). The role of genetic engineering, scientific priorities and research aims, and the enabling research and agricultural policy can be back-cast from each future scenario. Scenarios should be set in about 2015, a period beyond current research grants, the current Farm Bill, and corporate product pipelines, but near enough to influence policy and investment. The scenarios must include those that do not rely on GE crops but upon other approaches to agricultural sustainability goals.

Trait Value Analysis and Technology Roadmapping

The costs, benefits, and likely technical realization of traits must be estimated, measured, and modeled under various policy contexts as defined by the scenarios. Estimating the impact of any particular trait improvement must be considered within the possible biophysical variance of that trait under different cultivation conditions, its comparison to alternative approaches, and its value considered under different policy contexts. For example, a trait for improved nitrogen utilization may only have economic value or preference at a certain threshold of effectiveness within a context of certain nitrogen requirements, fertilizer costs, farming practice, and costs of nutrient pollution management. The previous steps of defining problems, future scenarios, and the value of specific traits will be used to create a technology roadmap. A technology development roadmap requires an assessment of the current state of knowledge, an assessment of trends in technical development, and a clear set of goals. Technology roadmapping is a process as well as a product that can engage many experts to identify critical enabling technologies and technical gaps needed to meet sustainability goals. A second common feature of technology roadmaps is planning for coordinated research activities that leverage R&D investments (Garcia and Bray 2002).

TABLE 5. A Possible Future Scenario for GE Crops in U.S. Commodity Agriculture?

Elements	Major Features of the Future Scenario
Production System	– Improved cultivation methods, genetically improved crops, policy for sustainability, and consumer demand drive the convergence of organic and genetically-improved production methods to a non-chemical, biology-based agricultural system. – U.S. agriculture is characterized by a much wider diversity of row crops, grown in rotations, with conservation tillage, cover crops, and inter-cropping that help manage soil fertility and retention. – Improved plant genetics allows greater resource productivity, reduced nutrient applications, reduced irrigation, and helps remove high-conservation value lands from production. – Disease- and pest-resistant plants and integrated pest management virtually eliminate use of chemical pesticides. – Varieties are optimized for livestock nutrition, healthy and lean animals, and minimal waste. – Anti-nutritionals in crops are greatly reduced.
Key Drivers	– Global pressure to eliminate subsidies and the advantage of foreign, low-cost producers drive the United States to be the world leader in high-value agricultural exports and commodities with high health and nutritional value. – Global commodity channels demand segregation of GE crops, which evolves into a competitive advantage for the United States. – Public opposition to GE risks and global market closures create incentives to improve safety, lower costs, and invest in public goods technologies for safety and sustainability. – Policy favors intellectual property sharing for public goods, payments for ecosystem goods and services, and raises the costs of pollution. – Investment in agricultural research increases with an emphasis on both U.S. and developing country needs. – Rising energy costs and climate change raise the cost of chemical and energy inputs, driving the move to renewable resources, and the value of carbon sequestration in soils and of biomass fuels.
Genetic Engineering	– Public opposition to GE crops drives R&D of design-for-environment features, ecological safeguards and targeted gene replacement, which lower costs, risks, and monopolization by large multinational companies. – Inter-phylum transgenic crops are replaced by intra-genus and intra-species gene replacement and site-directed optimization of complex traits. – Gene-targeting and design-for-environment strategies eliminate unintended gene flow and pleiotropic effects. – Transgenics become a tool for experimentation as high-throughput proteomics, genomics, and metabolic profiling accelerates marker-assisted breeding. – Complete integration of design for environmental and human safety elements shifts the focus to design for environmental sustainability and design for human health.

Box 2
What about Developing Countries?

The planning framework and conceptual approach of design-for-sustainability (including design-for-safety) is particularly important in the case of developing countries; this white paper is limited to the case of the United States with emphasis on commodity crops. Developing countries contain much of the world's biodiversity, almost all of the world's hunger and poverty, and the centers of origin and diversity of most major crops. In addition, environmentally sustainable production of locally adapted crops to improve the livelihoods of rural populations is a critical global need for which—in the long term—genetic engineering may be part of the solution. However, most of the world's poor countries have limited capacity for scientific research, genetic improvement of crops, and regulation of GE crops. Therefore, developing countries may benefit most from multiple mechanisms for environmental safety of GE crops, improved technologies that lower regulatory costs and oversight, and technologies for effective improvement of complex traits such as nutritional value, growth under stress, and post-harvest stability. The recommendations outlined below can provide a model for a similar analytic and planning process for regions and countries in the developing world to make their own decisions about whether and how to incorporate GE crops in their future agricultural systems.

WHY SECTORS CAN ALIGN BEHIND A SUSTAINABLE DESIGN AGENDA

Government and Society

The health of agro-ecosystems is vital to society, and the long-term, sustainable resource productivity of agriculture is fundamental to multiple U.S. interests. Political gridlock and acrimonious debates over GE crops divert energy within institutions that play much-needed roles in long-term U.S. and global agricultural development. Designing crops to address public perceptions of risks creates opportunity for beneficial products while addressing public calls for caution and more knowledge. For both the U.S. public and private sectors, R&D priorities for GE crops will continue to have significant ramifications on the agricultural and trade systems of the world. The U.S. government has near- and long-term needs to set priorities for U.S. national research investment and for investment priorities in research and regulatory capacity in developing countries. The social rate of return on investment in basic research (such as agricultural research) is estimated to be very high (Alston et al. 1998; ERS/USDA and ERS 2003). Since regulations due to scientific and societal concerns about genetic engineering safety increase the cost of GE crop research and development, designs that increase measurable and perceived product safety may be expected to have a high return on investment. A rigorous process of considering the future of GE crops will create preparedness for the potential social, economic, and policy issues presented by future generations of genetic engineering technology.

Private Biotechnology Companies

Agricultural biotechnology companies should have a significant interest in a strong public sector initiative in genetic engineering research and in supporting a research agenda and a policy agenda for sustainable agriculture. Issues and concerns related to agricultural biotechnology are leading to loss of markets, rising costs of regulations, and regulations for labeling and segregation that reduce incentives for product improvement and shake investor confidence. In partnership with a strong publicly-funded effort to address safety concerns, there may be a greater public acceptance of GE products and acceptance of the role and responsibilities of the private sector. A strong public effort to efficiently and transparently address public concerns will also relieve the private sector of a basic research role. Design elements to reduce gene flow, to create biological barriers to contain GE plants, and to aid segregation will reduce potential future corporate liabilities. Improved crops designed for sustainability may prevent future episodes such as the Monarch Butterfly controversy, and may reduce the risks of the human errors that led to the StarLink™ and ProdiGene contamination episodes.[11] Lastly, the research and development targets proposed here will require investment in emerging technologies and innovation—a true source of step-change increases in corporate value and competitive position (Day and Schoemaker 2000).

Farmers and U.S. Trade Interests

U.S. farm interests may also benefit by lending their political support to policy and research for agricultural sustainability. U.S. farmers, in the Midwest and elsewhere, have seen the dramatic closure of European and other markets to commodity exports, though coincident expansion in Latin America and China has masked this loss. Crops with built-in mechanisms for environmental safety and identity preservation may help open global markets to export crops and reduce potential liabilities throughout the value chain. The farmer may accept the additional cost of technologies incorporated in GE seeds that enhance environmental safety if those technologies lower the costs of compliance, refugia management and set-asides, and monitoring. Farmers also have a long-term interest in land stewardship and in eliminating the dangers of using toxic agricultural chemicals. Diversifying the crop mix and creating high-value commodities may increase farm incomes, buffer against commodity market fluctuations, and differentiate U.S. products from low-cost commodity production in countries such as Argentina, Brazil, and China.

The Basic Research Community

The basic research community may benefit from the increased public funding that results when research is aligned to important social and political goals—just as when national goals were set to eradicate polio, fight cancer, and sequence the human genome. A technology roadmap for GE crops will set high goals for discovery and innovation and integrate genetic engineering and its related fields into a broader R&D agenda. An effort to set research goals for genetic engineering for sustainability may also provide a model process for sustainability science and may lead to productive intersections of separate fields of scientific endeavor. Scientific efforts that are responsive to public concerns and that are well-communicated to the public will increase public trust and political support of science and increase the legitimacy of scientific institutions (ESRC 1999). There is resistance in the scientific community to scientific efforts that appear to address non-scientific public concerns, but in addressing such concerns, there is an opportunity for leadership from the scientific community to be the independent voice with a long-term view that is trusted by society. Strengthening public R&D in agricultural biotechnology can address needs for public goods genetic engineering research, discourage monopolization of technology and knowledge, support regulatory science, and inform the biotechnology debate.

Sustainable Development Interests

This white paper has focused on domestic U.S. agriculture. However, as the country with the greatest capacity to develop and test GE crops, an agenda for the future development of GE crops must also consider the risks, benefits, and context for developing countries. Enhancing the effectiveness and safety profile of the technical approach may make it more applicable for the areas of high biodiversity that exist in many tropical and sub-tropical developing regions and in the centers of origin for domesticated plants. Innovation to lower the cost of development, testing, and regulation is also likely to help develop appropriate and transferable technologies to developing countries. Design improvements may address cultural, religious, and ethical objections in other countries to transferring genes among species, ensure against poor regulatory enforcement, and may respect for small farmers' right to save and exchange seed. Developing countries also face pressing needs to manage pests and disease, reduce the burden of agricultural labor, conserve water, promote soil fertility, reduce vulnerability to shocks such as drought and disease, and compete in global markets. Poor farmers may realize greater marginal benefits from innovations that reduce dependence on external inputs, mechanization, and irrigation. Given developing countries' limited resources for development and science, the approach advocated in this white paper may also be a model and framework for establishing scientific and capacity-building priorities in these countries.

Conclusions and Recommendations

Policies and additional research and investment are needed to ensure that the role of genetic engineering in the future of U.S. agriculture supports economic, environmental, and social well-being. The potential of chemical-intensive agriculture, integrated agriculture, organic agriculture, or biotechnology-based agriculture to meet future human needs is hotly debated, but is not well-informed by a strongly substantiated, data-driven analysis of relative future costs, risks, and benefits, such as the one that would emerge from the process described above. Markets for GE crops designed for sustainability will only develop with appropriate planning and broad participation within a favorable policy context of trusted regulatory agencies, incentives for more sustainable agriculture, and research investment toward long- term goals.

The political barriers to creating an R&D agenda and policy environment that promotes the safety and sustainability contributions of GE crops are considerable. Established agricultural interests are reluctant to acknowledge the unsustainable aspects of U.S. agriculture in general and Midwestern agriculture in particular, especially the impacts of subsidies, over-production, and chemical inputs. The leading agricultural biotechnology companies are also agro- chemical companies and thus are reluctant to directly address the risks of chemically intensive agriculture. The intellectual property environment in the United States is designed for the appropriation of publicly developed technologies by private commercial interests and may not favor investment in technologies for public needs for which there are not yet markets.

Despite these obstacles, powerful shared interests are primed to motivate actors in the public and private sectors to partner in pursuit of sustainable agriculture goals. A better coordinated national R&D policy for agriculture and genetic engineering is needed—one that reflects what society most needs agriculture to accomplish, is guided by goals of agricultural sustainability, and presents a vision of a U.S. agricultural future that diverse sectors of society can align behind.

To plan for and take action to integrate genetic engineering with the goals of sustainable agriculture, this paper outlines recommendations for key stakeholder groups.

- **National agriculture R&D strategies should be strengthened by incorporating targets for agricultural sustainability. Inter-agency cooperation among those charged with scientific assessment, basic research, and applied agricultural research and technology development should be a prominent feature of such strategies.** For the agencies that regulate biotechnology—the U.S. Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration—there is an enormous need and opportunity for increased research coordination as well as restructuring and expansion. There is a similar opportunity for research coordination and shared goals among the agencies that fund basic research and technology development in plant molecular genetics, ecology, and environmental studies, including the National Institutes of Health, the National Science Foundation, and the Department of Energy.

- **Agricultural biotechnology companies should provide technical and political support for development of a research agenda and a policy agenda for integrating genetic engineering with the goals of a transition to sustainable agriculture.** These companies have a significant stake in partnering in a strong public-sector initiative that efficiently and transparently addresses safety and sustainability concerns about GE crops. Upstream efforts to improve design-for-safety and design-for-sustainability of GE crops are likely to benefit biotech companies by lowering product development and regulatory costs, shortening the time to market, boosting public acceptance of GE products, and reducing future corporate liabilities.

- **U.S. farmers and agricultural trade interests should lend their support to policies and research linking crop genetic engineering and agricultural sustainability.** Crops with built-in mechanisms for environmental safety and sustainability could help open global markets to export crops and differentiate U.S. products from low-cost commodity production. With their long-term interest in the stewardship of land and water resources, farmers and agricultural trade interests can provide a powerful voice for design-for-safety and design-for- sustainability goals of policy and investment in R&D for GE crops.

- **The basic research community has an opportunity to provide leadership and an independent voice for discovery and innovation to integrate genetic engineering and the long-term goals of U.S. agriculture.** Basic research often flourishes where scientific investigation becomes aligned with important social and economic goals, such as the setting of national goals to eradicate polio, explore the outer reaches of the solar system, or sequence the human genome. An effort to set research goals for genetic engineering that supports the transition to agricultural sustainability could provide a model process for sustainability science and lead to productive intersections of separate fields of scientific endeavor.
- **The international development community should also support an agenda for the future development of GE crops that considers the risks, benefits, and context for developing countries.** The planning framework and conceptual approach outlined in this paper focus on U.S. domestic agriculture. Developing countries, however, are home to much of the world's biodiversity and to almost all of the world's hunger, preventable disease, and poverty. Enhancing the design characteristics of GE crops to optimize safety and sustainability could make these crops more appropriate for use in tropical and sub-tropical developing regions, including areas of high biodiversity value and the centers of origin for domesticated plants. Given developing countries' limited resources for development and science, the approach described here may also be a model and framework for establishing scientific and capacity- building priorities in these countries.

The aligned interests of the many stakeholder groups—including farmers, agricultural biotechnology companies and other private-sector interests, federal and state regulatory agencies and research agencies, the scientific community, and nongovernmental organizations—can forge political support to provide answers to the question of how genetic engineering fits into the long-term goals for U.S. agricultural sustainability. It is too early to tell how genetic engineering of crops will be part of the transition to sustainability or how large a role it will play in the food, fiber, materials, and energy systems of the future. It is certain, however, that such a powerful technology merits thoughtful deployment and must be designed to respect public concerns and to address our most pressing needs. A sustainability-based plan for crop improvement has the potential to guide scientific discovery, stimulate product innovation, and inform policy formulation and more constructive public debate to ensure that the crops of the future will safely, effectively, and sustainability serve humanity and the U.S. economy. To create such a plan and to achieve these ends, the following actions are recommended:

- **An independent analysis and futures planning process to better inform decisions about how to apply genetic engineering to the future agricultural systems of the United States.** This process must be created by a partnership of private, state, and federal organizations that focuses upon scientific research and policy for agriculture and plant genetics and that involves other stakeholders in agriculture as well as nongovernmental organizations.
- **A quantitative risk-benefit assessment of the potential impacts of safety traits and sustainability traits achieved through modern crop breeding and genetic engineering approaches and deployed in different cultivation conditions and under different policy and market conditions.** The analysis must also consider the impact of high-value output traits for food, feed, and chemicals upon the commodity-handling system and farm economics as well as theoretical and experimental study of the impact of environmental stress tolerance traits upon plant fitness, ecological competition, and agricultural markets. Ultimately emerging from such a process of multi-stakeholder, multi-expert analysis and planning will be a technology roadmap that promotes coordinated research activities and leverag-

ing of R&D investments in genetic engineering for agricultural sustainability.

- **Increased federal financing to support public goods research for agricultural biotechnology that would not otherwise be undertaken by private corporations.** The first priority should be development of design-for-safety traits to enable subsequent investment in traits that impact agricultural environmental sustainability and human health. Public-private consortia may be appropriate to invest in technologies that are long-term, economically risky, or lack large markets, but are in the long-term interests of the agricultural system.

***Don S. Doering**, formerly a Senior Associate with the Sustainable Enterprise Program at the World Resources Institute, is now a Senior Associate at Winrock International. He is a member of the UN Millennium Project Hunger Task Force, the Commission of Environmental Cooperation's Maize Advisory Group, the Monsanto Biotechnology Advisory Council, and the board of directors of the Institute for Forest Biotechnology.*

Notes

1. A plant or other organism with genetics intentionally engineered by recombinant DNA techniques to create a specific trait is referred to here as genetically engineered (GE).

2. This white paper contains technical terminology from the fields of molecular biology, plant science, and agriculture. Definitions of these terms may be found at several excellent on-line resources including the Life Science Dictionary (on-line at: http://biotech.icmb.utexas.edu/search/dict-search.html), the Glossary of Biotech Terms (on-line at: http://biotechterms.org/), The FAO Glossary of Biotechnology for Food and Agriculture (on-line at: http://www.fao.org/biotech/index_glossary.asp?lang=en), the U.S. Department of Agriculture Sustainable Agriculture: Definitions and Terms (on-line at: http://www.nal.usda.gov/afsic/AFSIC_pubs/srb9902.htm), and the U.S. Department of Energy Genome Glossary (on-line at: http://www.ornl.gov/sci/techresources/Human_Genome/glossary/).

3. Maize and Biodiversity: The Impacts of Transgenic Maize in Mexico, draft report at http://www.cec.org/maize/resources/chapters.cfm?varlan=english.

4. Cartagena Protocol on Biosafety, available on-line at: http://www.biodiv.org/biosafety/default.aspx. Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed and Regulation (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC, available on-line at: http://europa.eu.int/eur-lex/en/search/search_lif.html.

5. The discussion in this white paper follows the National Research Council's analysis of transgenic plants, in which risk is interpreted as a blend of the probability of occurrence of some hazard and the consequence of a hazard being realized. Combining hazard and occurrence to characterize risk can be a highly subjective component of risk analysis when it incorporates some social criterion (NRC 2002); the term "safety" provides a useful focus for this discussion and for policy formulation.

6. There are no accurate measures of this cost; the estimate used in this white paper is based upon industrial R&D budgets and the costs of public sector initiatives. Estimates are confounded by the indeterminate boundaries among R&D, regulatory field trials, and commercial field trials as well as by the accounting of investments in research infrastructure. Costs will also vary considerably based upon the trait and required safety testing.

7. New methods of increasing transformation efficiency are under development to replace negative selection markers, including efficient transformant regeneration, positive selection, improved Agrobacterium tumefaciens, and rapid screening (Zuo et al. 2002; De Vetten et al. 2003). Marker excision methods include co-transformation of unlinked transgenes and markers that can be excised by site-specific and inducible enzymes (Hohn et al. 2001; Ow 2001; Zuo et al. 2001; Hare and Chua 2002). Transgene deletion has inspired a design concept to address issues of food safety, gene flow, identity preservation, and intellectual property in which the transgene is selectively removed from pollen, edible fruit, or seeds (Keenan and Stemmer 2002).

8. Apomixis technology may create a mechanism of environmental containment and allow poor farmers to retain high quality transgenic seed yet may also threaten private sector interests in control of germplasm (Shoemaker 2001; Charles 2003).

9. Many transgenic approaches have been taken toward tolerance of heat, chilling, and freezing with modest success and have confirmed that temperature tolerance is a complex trait (Sung et al. 2003). High-throughput studies of gene expression have identified more than 300 genes induced by drought, temperature, or salinity and 40 inducible transcription factor genes (Seki et al. 2003).

10. U.S. national efforts must also support and be coordinated with international processes such as the nascent International Assessment of Agricultural Science and Technology for Development (IAASTD) sponsored by Food and Agriculture Organization of the United Nations (FAO), United Nations Development Program (UNDP), United Nations Environment Programme (UNEP), United Nations Educational, Scientific and Cultural Organization (UNESCO),World Bank (WB), and the World Health Organization (WHO). On-line at http://www.agassessment.org/index.html.

11. The StarLink™ contamination episode began in October 2000 when traces of a genetically modified corn variety called StarLink™, marketed by Aventis, showed up in taco shells in the U.S. even though it was only approved for animal feeds and was not approved for human consumption. The discovery led to a massive recall of over 300 food brands and significant transient declines in corn prices. The ProdiGene episode refers to violations of two field test permits issued to the Texas-based biotechnology company for development of corn varieties genetically engineered to produce pharmaceutical proteins. In both cases, the violations involved failure to adequately destroy GE corn plants and seed from 2001 field trials, thereby contaminating crops grown on the sites in 2002.

Glossary

Abiotic stresses	Stress experienced by crop plants because of non-living, environmental factors such as cold, heat, drought, flooding, salinity, toxic metals, and ultraviolet-B light. *[From biotechterms.org]*
Allele	One of several alternate forms of a gene occupying a given location on the chromosome. *[From biotechterms.org]*
Anti-nutritional compound	Compound in food or feed that has a negative impact on nutrition or the absorption of other nutrients.
Apomixis	The ability of some plant species to reproduce asexually through seeds. In apomixis, embryos develop without the contribution of a male gamete. The result is that apomictically produced seeds inherit their genes exclusively from the mother plant.
Arabidopsis thaliana	A small plant in the mustard (Brassicaceae) family. With very little repetitive DNA in its genome, Arabidopsis is used as a model for studying plant genetics. At least two genetic maps have been created for Arabidopsis thaliana.
Brassica	A plant family that includes rape, cabbage, broccoli, kale, cauliflower, and watercress.
Conservation tillage	A term that covers a broad range of soil tillage systems that leave residue cover on the soil surface, substantially reducing the effects of soil erosion from wind and water. *[From www.nal.usda.gov]*
Down regulate	Refers to the action of a DNA sequence or other chemical compound that causes a given gene to express less of the protein that it normally codes for. *[From biotechterms.org]*
Drought tolerance trait	Refers to any trait whereby a given plant is able to survive a prolonged period of little or no rainfall.
Elite germplasm	Refers to pure-breeding, well-characterized germplasm that is adapted (selectively bred) and optimized to new environmental conditions.
Eutrophication	A process in which bodies of water (such as lakes, estuaries, or slow-moving streams) receive excess fertilizers and other nutrients that stimulate excessive plant growth, reducing dissolved oxygen levels and often causing the death of other aquatic organisms.
Expression (of genes)	The means by which a gene's information stored in DNA is turned into biochemical information such as RNA or protein.
Exudate enzymes	Enzymes found in root exudates, the complex mixture of proteins and other chemical compounds produced by the interaction of secreted plant root compounds and micro-organisms in the rhizosphere.
Gene	A natural unit of the hereditary material, which is the physical basis for the transmission of the characteristics of living organisms from one generation to another. The basic genetic material of all living organisms consists of chain-like molecules of nucleic acids—deoxyribonucleic acid (DNA) in most organisms and ribonucleic acid (RNA) in certain viruses. *[From biotechterms.org]*
Gene conversion	A process during which one allele is replicated at the expense of another, leading to non-Mendelian segregation ratios, also the targeted or random change of an allele through mutagenesis.
Gene delivery	The insertion of genes (e.g., via bacterial or viral vectors) into selected cells.

Glossary, continued

Gene flow	The spread of genes from one breeding population to another (usually) related population, thereby generating changes in allele frequency.
Gene splicing	The enzymatic attachment (joining) of one gene (or part of a gene) to another. *[From biotechterms.org]*
Gene targeting	The insertion of DNA sequences in vivo into selected cells or at selected chromosomal locations in order to add new genes or to modify the activity of existing genes. See also gene delivery. *[From biotechterms.org]*
Genetic marker	Refers to a segment of DNA (e.g., gene) within an organism's overall DNA that is a reliable indicator that that particular organism possesses a specific trait of interest. Markers may be used to select certain organisms, e.g., those cells that have inherited resistance to an antibiotic will be the only ones in a population that survive antibiotic treatment.
Genetic Use Restriction Technologies (GURTs)	A general term referring to several different technologies intended to control the expression (or non-expression) of the gene(s) for specific traits. GURTs may be applied to limit the expression of transgenes for safety or commercial purposes.
Genome	The entire hereditary material (DNA) in a cell. In addition to the DNA contained in the cell nucleus (known as nuclear DNA), an organism's cells contain some DNA in other locations, including chloroplasts (plants) and mitochondria (animals). *[From biotechterms.org]*
Genotype	The total genetic, or hereditary, constitution that an individual receives from its parents. An individual organism's genotype is distinguished from its phenotype, which is its appearance or observable character. *[From biotechterms.org]*
Germplasm	The total genetic variability of an organism, represented by the total available pool of germ cells or seed. Also used to refer to the total collection of seed of a species. *[From biotechterms.org]*
Herbicide-tolerant crop	A crop plant that has been altered to be able to survive application(s) of one or more herbicides by the incorporation of certain gene(s), via either genetic engineering, natural mutation, or mutation breeding. *[From biotechterms.org]*
High-throughput screening	Automated systems designed to process large numbers of tests that identify a desired genetic trait.
Identifier sequence	A uniquely identifiable DNA sequence.
Inducible gene	A gene that is expressed only in the presence of a specific compound, the inducer, which may be produced internally or applied externally to the cell.
Input trait	A trait that reduces the level of agricultural inputs such as those chemicals required for the control of insects, diseases, and weeds in a given agricultural crop.
Insertion site (genomic)	A unique site in a DNA molecule or chromosome into which foreign DNA is inserted. *[From fao.org]*
Instability (of transgenes)	A lack of consistent phenotype or genotype, usually as a result of uncontrolled changes in gene expression or from genetic changes caused by mobile genetic elements or genetic structures not tolerated by the organism's DNA repair mechanisms.
Introgression	The introduction of new alleles or genes into a population from an exotic source, usually another species. *[From fao.org]*

Glossary, continued

Landrace	In plant genetic resources, an early, cultivated form of a crop species, evolved from a wild population, and genetically heterogeneous. *[From fao.org]*
Marker gene	See genetic marker.
Marker-assisted breeding	See marker-assisted selection.
Marker-assisted selection	The use of DNA sequence "markers" to select the organisms that possess gene(s) for a particular performance trait (e.g., rapid growth, high yield, etc.) desired for subsequent breeding/propagation. This allows selection without having to screen for the performance trait itself, which may be difficult or only occur under certain conditions or after long periods of time.
Maternal inheritance	Inheritance controlled by non-nuclear genes (e.g., found in the mitochondria or chloroplasts) that are transmitted only through the female line. *[From fao.org]*
Mendelian inheritance	See Mendelian segregation.
Mendelian segregation	Occurs when alleles are inherited according to Mendel's Laws. The Law of Segregation states that each hereditary characteristic is controlled by two "factors" (now called alleles), which segregate independently and pass into separate germ cells. *[From fao.org]*
mRNA	Abbreviation for messenger RNA, a molecule produced by transcription of a protein-encoding gene. The information encoded in mRNA is translated into a gene product by the ribosomes. *[From fao.org]*
Metabolite profiling	Determination of which metabolic pathways (and/or related genes) are "switched on" within a cell, tissue, or organism, thereby enabling definition of the response to an environmental stimulus or a genetic modification. *[From biotechterms.org]*
Mobile genetic element	A genetic element that inserts into a chromosome, excises itself, and then relocates with the organism's genome, such as the transposable elements of corn.
Mutagen	A chemical substance capable of producing a genetic mutation (change), by causing changes in the DNA of living organisms. *[From biotechterms.org]*
Mutation hotspot	A genetic sequence with a very high frequency of mutation.
Negative selection	Selection against individuals possessing a certain character. *[From fao.org]*
Output trait	A trait of agricultural crops that enhances the quality of food and/or fiber products derived from that crop.
Overexpression (of transgene)	Up-regulation of expression beyond normal physiological levels.
Phenotype	The visible appearance of an individual (with respect to one or more traits) which reflects the reaction of a given genotype with a given environment. *[From fao.org]*
Pleiotropic	An adjective used to describe a gene that affects more than one (apparently unrelated) characteristic of the phenotype, such as a single gene that affects flowering, leaf shape, and growth rates. *[From biotechterms.org]*
Promoter	A region of DNA located "upstream" of a gene that controls to what degree, where (e.g., which portion of a plant), and when (e.g., which life stage of an organism) that gene is expressed. The promoter's impact on the timing/degree of gene expression is itself regulated by the molecules that bind to the promoter. *[From biotechterms.org]*

Glossary, continued

Proteomics	The scientific study of an organism's proteins and their role in an organism's structure, growth, and health. *[From biotechterms.org]*
Rhizosphere	The soil region in the immediate vicinity of growing plant roots. [From fao.org]
Seed lethality	A trait that kills the seed.
Selectable marker	See genetic marker.
Trait	A characteristic of an organism, which manifests itself in the phenotype (physically). Many traits are the result of the expression of a single gene, but some are polygenic, or "complex," resulting from simultaneous expression of more than one gene. *[From biotechterms.org]*
Transgene	A gene that is inserted into the genome of a cell via gene splicing techniques. *[From biotechterms.org]*
Up-regulate	Refers to the action of a DNA sequence or other chemical compound that causes a given gene to express more of the protein that it normally codes for.
Viral transgene promoter	A promoter of a transgene that came from a virus.
Volunteer plant	A plant arising from seed dispersed from a previous crop.
Weediness	The ability of a plant to colonize a disturbed habitat and compete with cultivated species. *[From fao.org]*
Yield drag	The difference in yield between crop varieties, e.g., between a lower-yielding genetically engineered plant and its conventional counterpart.

Definitions included in this glossary were adapted from several online sources, including The Glossary of Biotech Terms (http://biotechterms.org), the FAO Glossary of Biotechnology for Food and Agriculture (www.fao.org/biotech/index_glossary.asp?lang=en), and the USDA's Sustainable Agriculture: Definitions and Terms (www.nal.usda.gov/afsic/AFSIC_pubs/serb9902.htm).

References

Alston, J.M., G. Norton, and P.G. Pardey. 1998. *Science under Scarcity: Principles and Practice for Agricultural Research and Priority Setting*. Wallingford, UK: CAB International.

Alvarez-Buylla, E.R. 2003. "Ecological and Biological Aspects of the Impacts of Transgenic Maize, Including Agro-Biodiversity." Montreal, Canada: Commission for Environmental Cooperation of North America. June 1, 2003. On-line at: http://www.cec.org/files/PDF//Alvarez-Buylla-e.pdf.

Apse, M., and E. Blumwald. 2002. "Engineering Salt Tolerance in Plants." *Current Opinion in Biotechnology* 13(2):146-150.

Arnold, T. 2003. "DuPont Agriculture and Nutrition." Wilmington, DE: The DuPont Company. February 27, 2003. On-line at: http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=DD&script=1200

[ASA] American Soybean Association. 2001. "Conservation Tillage Study." St. Louis, MO: American Soybean Association. November 12, 2001. On-line at: http://www.soygrowers.com/ctstudy/ctstudy_files/frame.htm.

Atkinson, R.C., R.N. Beachy, G. Conway, F.A. Cordova, M.A. Fox, K.A. Holbrook, D.F. Klessig, R.L. McCormick, P.M. McPherson, H.R. Rawlings, 3rd, R. Rapson, L.N. Vanderhoef, J.D. Wiley, and C.E. Young. 2003. "Intellectual Property Rights: Public Sector Collaboration for Agricultural IP Management." *Science* 301(5630):174-175.

Beachy, R.N. 2003. "IP Policies and Serving the Public." *Science* 299(5606):473-.

Bennett, L.E., J.L. Burkhead, K.L. Hale, N. Terry, M. Pilon, and E.A. Pilon-Smits. 2003. "Analysis of Transgenic Indian Mustard Plants for Phytoremediation of Metal-Contaminated Mine Tailings." *Journal of Environmental Quality* 32(2):432-440.

Beus, C.E., and R.E. Dunlap. 1990. "Conventional Versus Alternative Agriculture: The Paradigmatic Roots of the Debate." *Rural Sociology* 55(4):590-616.

Bizily, S.P., C.L. Rugh, and R.B. Meagher. 2000. "Phytodetoxification of Hazardous Organomercurials by Genetically Engineered Plants." *Nature Biotechnology* 18(2):213-217.

Bowman, D.T., O.L. May, and J.B. Creech. 2003. "Genetic Uniformity of the US Upland Cotton Crop Since the Introduction of Transgenic Cottons." *Crop Science* 43:515-518.

Brinch-Pedersen, H., L.D. Sorensen, and P.B. Holm. 2002. "Engineering Crop Plants: Getting a Handle on Phosphate." *Trends in Plant Science* 7(3):118-125.

Britt, A., and G. May. 2003. "Re-engineering Plant Gene Targeting." T*rends in Plant Science* 8(2):90-95.

Carpenter, J., A. Felsot, T. Goode, M. Hammig, D. Onstad, and S. Sankula. 2002. *Comparative Environmental Impacts of Biotechnology-Derived and Traditional Soybean, Corn, and Cotton Crops*. Ames, Iowa: Council for Agricultural Science and Technology. June 2002.

Carpenter, J.E. 2001. "Comparing Roundup Ready and Conventional Soybean Yields." Washington, D.C.: National Center for Food and Agricultural Policy. January 2001.

[CBO] Congressional Budget Office. 2002. "Pay-As-You-Go Estimate H.R. 2646 Farm Security And Rural Investment Act of 2002." Washington, D.C.: Congressional Budget Office. May 22, 2003. On-line at: http://www.cbo.gov/showdoc.cfm?index=3468&sequence=0.

[CDC] Centers for Disease Control and Prevention. 2001. *Investigation of Human Health Effects Associated with Potential Exposure to Genetically Modified Corn.* Atlanta: Centers for Disease Control and Prevention. June 11, 2001. On-line at: http://www.cdc.gov/nceh/ehhe/Cry9cReport/cry9cre-port.pdf.

Charles, D. 2003. "Corn that Clones Itself." *Technology Review* (March 2003):33-41.

Clark, W.C. 2002. "Science and Technology for Sustainable Development." Science and Technology for Sustainable Development, Mexico City, Mexico, Initiative on Science and Technology for Sustainability. May 20-23, 2002.

Cockburn, A., and R. Phipps. 2003. "GM Technology: A Tool to Benefit Livestock Production in Less Developed and Developed Countries." London, UK: British Society for Animal Science. On-line at: http://www.bsas.org.uk/meetings/annlproc/Pdf2003/210.pdf.

Crawley, M. 2003. "Will GM Crops and Their Hybrids Become Invasive? GM Crops, Modern Agriculture and the Environment." London, The Royal Society. February 11, 2003.

Crawley, M.J., S.L. Brown, R.S. Hails, D.D. Kohn, and M. Rees. 2001. "Transgenic Crops in Natural Habitats." *Nature* 409(6821):682-683.

CropLife. 2002. "Facts and Figures: Global Market 2002." CropLife International. Cited July 11, 2003. On-line at http://www.croplife.org/web-site/pages/facts_and_figures_2002.aspx.

Dale, P.J., B. Clarke, and E.M. Fontes. 2002. "Potential for the Environmental Impact of Transgenic Crops." *Nature Biotechnology* 20(6):567-574.

Daniell, H. 1999. "GM Crops: Public Perception and Scientific Solutions." *Trends in Plant Science* 4(12):467-469.

Daniell, H. 2002. "Molecular Strategies for Gene Containment in Transgenic Crops." *Nature Biotechnology* 20(6):581-586.

Day, G.S. and P.J.H. Schoemaker. 2000. *Wharton on Managing Emerging Technologies.* New York, NY: John Wiley and Sons, Inc.

De Vetten, N., A.M. Wolters, K. Raemakers, I. Van Der Meer, R. Ter Stege, E. Heeres, P. Heeres, and R. Visser. 2003. "A Transformation Method for Obtaining Marker-Free Plants of a Cross-Pollinating and Vegetatively Propagated Crop." *Nature Biotechnology* 21(4):439-442.

[DEFRA] United Kingdom Department for Environment, Food, and Rural Affairs. 2001. "Guidance on Principles of Best Practice in the Design of Genetically Modified Plants." Department for Environment, Food & Rural Affairs, Advisory Committee on Releases to the Environment. Cited May 22, 2002. On-line at http://www.defra.gov.uk/environment/acre/best-prac/guidance/index.htm.

Dower, R., D. Ditz, P. Faeth, N. Johnson, K. Kozloff, and J.J. MacKenzie. 1997. *Frontiers of Sustainability: Environmentally Sound Agriculture, Forestry, Transportation, and Power Production*. Washington, DC: World Resources Institute.

Ellstrand, N. 2001. "When Transgenes Wander, Should We Worry?" *Plant Physiology* 125(1543-1545).

Ellstrand, N.C. 2003. *Dangerous Liaisons? When Cultivated Plants Mate with Their Wild Relatives.* Baltimore, MD.: Johns Hopkins University Press.

[EPA] U.S. Environmental Protection Agency. 2000. *Assessment of Scientific Information Concerning StarLink™ Corn.* SAP Report No. 2000-06. Washington, DC.: U.S. Environmental Protection Agency. December 1, 2000. On-line at: http://www.epa.gov/scipoly/sap/2000/november/one.pdf.

EPA. 2001. *Assessment of Additional Scientific Information Concerning StarLink™ Corn.* SAP Report No. 2001-09. Washington, DC.: U.S. Environmental Protection Agency. July 2001. On-line at: http://www.epa.gov/oscpmont/sap/2001/july/julyfinal.pdf.

EPA. 2003. *Inventory Of U.S. Greenhouse Gas Emissions And Sinks: 1990 - 2001.* EPA 430- R-03-004. Washington, DC.: U.S. Environmental Protection Agency. April 2003. On-line at: http://www.epa.gov/oscpmont/sap/2001/july/julyfinal.pdf.

[ERS/USDA] Economic Research Service of the U.S. Department of Agriculture. 2003. *Agricultural Resources and Environmental Indicators.* Washington, DC: United States Department of Agriculture Economic Research Service. February 2003.

[ESRC} Economic and Social Research Council of the United Kingdom. 1999. "The Politics of GM Food: Risk, Science and Public Trust." Special Briefing No. 5. University of Sussex: ESRC Global Environment Change Programme.

[ESA] Ecological Society of America. 2004. "Genetically Engineered Organisms and the Environment: Current Status and Recommendations." Washington, DC: Ecological Society of America. February 2004. On-line at: http://www.esa.org/pao/esaPositions/Papers/geo_position.htm

[EU] European Union. 1997. Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 Concerning Novel Foods and Novel Food Ingredients. Official Journal L043(14/02/1997):0001-0006.

[FAO/WHO] Food and Agricultural Organization/World Health Organization. 1996. *Biotechnology and Food Safety: A Report of a Joint FAO/WHO Consultation*. Rome, Italy: World Health Organization. 30 September - 4 October 1996. On-line at: http://www.fao.org/es/ESN/food/pdf/biotechnology.pdf.

FAO/WHO. 2000. *Safety Aspects of Genetically Modified Foods of Plant Origin: Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology.* Geneva, Switzerland: World Health Organization. 29 May - 2 June 2000.

Fawcett, R., and D. Towery. 2002. *Conservation Tillage and Plant Biotechnology.* West Lafayette, IN: Conservation Technology Information Center.

Fernandez-Cornejo, J., and W.D. McBride. 2000. "Genetically Engineered Crops for Pest Management in U.S. Agriculture: Farm-Level Effects." No. 786. Washington, DC: U.S. Department of Agriculture, Economic Research Service. April 2000.

Fernandez-Cornejo, J. and C. Hendricks. 2003. "Off-Farm Work and the Economic Impact of Adopting Herbicide-Tolerant Crops." Montreal, Canada: American Agricultural Economics Association Annual Meeting, July 27-30, 2003. On-line at http://agecon.lib.umn.edu/cgi-bin/pdf_view.pl?paperid=8772&ftype=.pdf.

Firbank, L.G., J.N. Perry, G.R. Squire, D.A. Bohan, D.R. Brooks, G.T. Champion, S.J. Clark, R.E. Daniels, A. M. Dewar, A.J. Haughton, C. Hawes, M.S. Heard, M.O. Hill, M.J. May, J.L. Osborne, P. Rothery, D.B. Roy, R.J. Scott, and I.P. Woiwod. 2003. "The Implications of Spring-Sown Genetically Modified Herbicide-Tolerant Crops for Farmland Biodiversity: A Commentary on the Farm Scale Evaluations of Spring-Sown Crops." U.K. Department for Environment, Food and Rural Affairs. On-line at: http://www.defra.gov.uk/environment/gm/fse/index.htm

Fischer, R., and U. Commandeur. 2003. "Biosafety Aspects of Molecular Farming." The International Symposium on The Biosafety of Genetically Modified Organisms, Beijing, China.

Fraley, R.T. 2003. "Field of Dreams Tour 2003." Monsanto Company. Cited June 16, 2003. On-line at http://media.corporate-ir.net/media_files/NYS/MON/presentations/MON_061303.pdf.

Freese, B. 2002. "Manufacturing Drugs and Chemicals in Crops: Biopharming Poses New Threats to Consumers, Farmers, Food Companies and the Environment." July 2002. Available on-line at www.foe.org/camps/comm/safefood/biopharm/BIOPHARM_REPORT.pdf

[GAO] General Accounting Office. 1999. *Water Quality: Federal Role in Addressing and Contributing to Nonpoint Source Pollution*. GAO/RCED-99-45. Washington, DC: U.S. General Accounting Office. February 1999.

Garcia, M.L., and O. Bray. 2002. "Fundamentals of Technology Roadmapping." Sandia National Laboratories. Cited March 25, 2003. On-line at http://www.sandia.gov/Roadmap/home.htm#exec.

Gerhardson, B. 2002. "Biological Substitutes for Pesticides." *Trends in Biotechnology* 20(8):338-343.

Goolsby, D., and W. Battaglin. 2000. "Nitrogen in the Mississippi Basin: Estimating Sources and Predicting Flux to the Gulf of Mexico." U.S. Geological Survey Fact Sheet 135-00. Washington, DC: U.S. Geological Survey. December 2000.

Gressel, J., and G. Ehrlich. 2002. "Universal Inheritable Barcodes for Identifying Organisms." *Trends in Plant Science* 7(12):542-544.

Gurian-Sherman, D. 2003. "Holes in the Biotech Safety Net." Washington, DC: Center for Science in the Public Interest. January 7, 2003.

Hanin, M., and J. Paszkowski. 2003. "Plant Genome Modification by Homologous Recombination." *Current Opinion in Plant Biology* 6(2):157-162.

Hare, P.D., and N.H. Chua. 2002. "Excision of Selectable Marker Genes from Transgenic Plants." *Nature Biotechnology* 20(6):575-580.

Heap, I. 2003. "The International Survey of Herbicide Resistant Weeds." Herbicide Resistance Action Committee. Cited June 20, 2003. On-line at www.weedscience.com.

Heinz. 2002. *The State of the Nation's Ecosystems*. Washington, DC: The H. John Heinz III Center for Science, Economics and the Environment.

Hell, R., and H. Hillebrand. 2001. "Plant Concepts for Mineral Acquisition and Allocation." *Current Opinion in Biotechnology* 12(2):161-168.

Hin, C.J.A., P. Schenkelaars, and G.A. Pak. 2001. *Agronomic and Environmental Impacts of the Commercial Cultivation of Glyphosate Tolerant Soybean in the USA.* Utrecht, Netherlands: Centre for Agriculture and Environment. June 2001.

Hirsch, R.E., and M.R. Sussman. 1999. "Improving Nutrient Capture from Soil by the Genetic Manipulation of Crop Plants." *Trends in Biotechnology* 17(9):356-361.

Hohn, B., A. Levy, and H. Puchta. 2001. "Elimination of Selection Markers from Transgenic Plants." *Current Opinion in Biotechnology* 12(2):139-143.

Hohn, B., and H. Puchta. 2003. "Some Like It Sticky: Targeting of the Rice Gene Waxy." *Trends in Plant Science* 8(2):51-53.

Horrigan, L., R.S. Lawrence, and P. Walker. 2002. "How Sustainable Agriculture Can Address the Environmental and Human Health Harms of Industrial Agriculture." *Environmental Health Perspectives* 110(5):445-456.

Hubbell, B.J. and R. Welsh. 1998. "Transgenic Crops: Engineering a More Sustainable Agriculture?" *Agriculture and Human Values* 15:43-56.

Initiative, A.G. 2000. "Analysis of the Genome Sequence of the Flowering Plant *Arabidopsis thaliana." Nature* 408(6814):796-815.

[ISB] Information Systems for Biotechnology. 2004. "Field Test Releases in the U.S. Information Systems for Biotechnology." Cited June 30, 2004. On-line at http://www.isb.vt.edu/cfdocs/fieldtests1.cfm.

Jaffe, G. 2003. "Planting Trouble: Are Farmers Squandering Bt Corn Technology?" Washington, DC: Center for Science in the Public Interest. June 19, 2003.

James, C. 2003. "Preview: Global Status of Commercialized Transgenic Crops: 2003." ISAAA Briefs No. 30. Ithaca, NY: The International Service for the Acquisition of Agri- biotech Applications (ISAAA). On-line at: www.isaaa.org.

Jaworski, J., and E.B. Cahoon. 2003. "Industrial Oils from Transgenic Plants." *Current Opinion in Plant Biology* 6(2):178-184.

Keenan, R.J., and W.P. Stemmer. 2002. "Nontransgenic Crops from Transgenic Plants." *Nature Biotechnology* 20(3):215-216.

King, D. 2003. *GM Science Review: First Report*. London, U.K.: GM Science Review Panel of the UK Government. July 21, 2003.

Kleter, G.A., W.M. van der Krieken, E.J. Kok, D. Bosch, W. Jordi, and L.J. Gilissen. 2001. "Regulation and Exploitation of Genetically Modified Crops." *Nature Biotechnology* 19(12):1105-1110.

Kuiper, H.A., G.A. Kleter, H.P. Noteborn, and E.J. Kok. 2001. "Assessment of the Food Safety Issues Related to Genetically Modified Foods." *The Plant Journal* 27(6):503-528.

Losey, J.E., L.S. Rayor, and M.E. Carter. 1999. "Transgenic Pollen Harms Monarch Larvae." *Nature* 399(6733):214.

Lyson, T.A. 2002. "Advanced Agricultural Biotechnologies and Sustainable Agriculture." *Trends in Biotechnology* 20(5):193-196.

McDonough, W. and Braungart, M. 1998. "The Next Industrial Revolution." The Atlantic Online. On-line at: http://www.theatlantic.com/issues/98oct/industry.htm.

Meagher, R. 2000. "Phytoremediation of Toxic Elemental and Organic Pollutants." *Current Opinion in Plant Biology* 3(2):153-162.

Monsanto. 2003. "Monsanto: Spring 2003 Investor Meetings." St. Louis, MO: Monsanto Company. May 12, 2003. On-line at: http://media.corporate-ir.net/media_files/NYS/MON/presentations/Investor_Background_Presentation.pdf.

Moore, I., L. Galweiler, D. Grosskopf, J. Schell, and K. Palme. 1998. "A Transcription Activation System for Regulated Gene Expression in Transgenic Plants." *Proceedings of the National Academy of Sciences USA* 95(1):376-381.

[NRC] National Research Council. 2000. *Genetically Modified Pest-Protected Plants: Science and Regulation*. Washington, DC: National Academy of Sciences, National Research Council.

NRC. 2002. *Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation*. Washington, DC: National Academy of Sciences, National Research Council.

NRC. 2004. *Biological Confinement of Genetically Engineered Organisms*. Washington, DC: National Academy of Sciences, National Research Council.

[NSB] National Science Board. 2002. *Science and Engineering Indicators - 2002*. Arlington, VA: National Science Foundation, National Science Board.

Oh, T., and G. May. 2001. "Oligonucleotide-Directed Plant Gene Targeting." *Current Opinion in Biotechnology* 12(2):169-172.

Ow, D.W. 2001. "The Right Chemistry for Marker Gene Removal?" *Nature Biotechnology* 19(2):115-116.

Paarlberg, R.L. 2001. "Environmentally Sustainable Agriculture in the 21st Century." Aspen Institute Congressional Program, 29 May – 2 June 2001. pp 29-36.

Padidam, M. 2003. "Chemically Regulated Gene Expression in Plants." *Current Opinion in Plant Biology* 6(2):169-177.

Persley, G.J. 2003. "New Genetics, Food and Agriculture: Scientific Discoveries - Societal Dilemmas." The International Council for Science. June 10, 2003.

Pew Initiative on Food and Biotechnology. 2002a. "Environmental Savior or Saboteur: Debating the Impacts of Genetic Engineering. Pew Initiative on Food and Biotechnology." Cited December 18, 2002. On-line at http://pewagbiotech.org/research/survey1-02.pdf.

Pew Initiative on Food and Biotechnology. 2002b. "Pharming the Field." Washington, DC, Pew Initiative on Food and Biotechnology. July 2002.

Priest, S.H. 2000. "US Public Opinion Divided over Biotechnology?" *Nature Biotechnology* 18(September):939-942.

Romer, S., P.D. Fraser, J.W. Kiano, C.A. Shipton, N. Misawa, W. Schuch, and P.M. Bramley. 2000. "Elevation of the Provitamin A Content of Transgenic Tomato Plants." *Nature Biotechnology* 18(6):666-669.

Ruiz, J.M. 2001. "Engineering Salt Tolerance in Crop Plants." *Trends in Plant Science* 6(10):451.

Ruiz, O.N., H.S. Hussein, N. Terry, and H. Daniell. 2003. "Phytoremediation of Organomercurial Compounds via Chloroplast Genetic Engineering." *Plant Physiology* 132(3):1344-1352.

Ruttan, V.W. 1999. "The Transition to Agricultural Sustainability." *Proceedings of the National Academy of Sciences USA* 96(11):5960-5967.

Saxena, D., and G. Stotzky. 2001. "*Bacillus thuringiensis* (Bt) Toxin Released from Root Exudates and Biomass of Bt Corn Has No Apparent Effect on Earthworms, Nematodes, Protozoa, Bacteria, and Fungi in Soil." *Soil Biology and Biochemistry* 33:1225-1230.

Schernthaner, J.P., S.F. Fabijanski, P.G. Arnison, M. Racicot, and L.S. Robert. 2003. "Control of Seed Germination in Transgenic Plants Based on the Segregation of a Two-Component Genetic System." *Proceedings of the National Academy of Sciences USA* 100(11):6855-6859.

Scriber, J.M. 2001. "Bt or not Bt: Is that the Question?" *Proceedings of the National Academy of Sciences USA* 98(22):12328-12330.

Sears, M.K., R.L. Hellmich, D.E. Stanley-Horn, K.S. Oberhauser, J.M. Pleasants, H.R. Mattila, B.D. Siegfried, and G.P. Dively. 2001. "Impact of Bt Corn Pollen on Monarch Butterfly Populations: A Risk Assessment." *Proceedings of the National Academy of Sciences USA* 98(21):11937-11942.

Seki, M., A. Kamei, K. Yamaguchi-Shinozaki, and K. Shinozaki. 2003. "Molecular Responses to Drought, Salinity and Frost: Common and Different Paths for Plant Protection." *Current Opinion in Biotechnology* 14(2):194-199.

Shewmaker, C.K., J.A. Sheehy, M. Daley, S. Colburn, and D.Y. Ke. 1999. "Seed-Specific Overexpression of Phytoene Synthase: Increase in Carotenoids and Other Metabolic Effects." *The Plant Journal* 20(4):401-412X.

Shi, H., B.H. Lee, S.J. Wu, and J.K. Zhu. 2003. "Overexpression of a Plasma Membrane Na(+)/H(+) Antiporter Gene Improves Salt Tolerance in *Arabidopsis thaliana." Nature Biotechnology* 21(1):81-85.

Shoemaker, R. 2001. "Economic Issues in Agricultural Biotechnology." No. 762. Washington, DC: U.S. Department of Agriculture, Economic Research Service. February 2001.

Singer, A., D. Crowley, and I. Thompson. 2003. "Secondary Plant Metabolites in Phytoremediation and Biotransformation." *Trends in Biotechnology* 21(3):123-130.

Smyth, S., G.G. Khachatourians, and P.W. Phillips. 2002. "Liabilities and Economics of Transgenic Crops." *Nature Biotechnology* 20(6):537-541.

Sneller, C.H. 2003. "Impact of Transgenic Genotypes and Subdivision on Diversity within Elite North American Soybean Germplasm." *Crop Science* 43:409-414.

Snow, A.A. 2002. "Transgenic Crops: Why Gene Flow Matters." *Nature Biotechnology* 20(6):542.

Snow, A.A., D. Pilson, L.H. Rieseberg, M. Paulsen, N. Plescak, M.R. Reagon, D.E. Woldf, and S.M. Selbo. 2003. "A Bt Transgene Reduces Herbivory and Enhances Fecundity in Wild Sunflowers." E*cological Applications* 13:279-286

Socolow, R.H. 1999. "Nitrogen Management and the Future of Food: Lessons from the Management of Energy and Carbon." *Proceedings of the National Academy of Sciences USA* 96(11):6001-6008.

[SOT] Society of Toxicology. 2002. "The Safety of Genetically Modified Foods Produced Through Biotechnology." Reston, VA: U.S. Society of Toxicology. September 25, 2002.

Stanley-Horn, D.E., G.P. Dively, R.L. Hellmich, H.R. Mattila, M.K. Sears, R. Rose, L.C. Jesse, J.E. Losey, J.J. Obrycki, and L. Lewis. 2001. "Assessing the Impact of *Cry1Ab*- Expressing Corn Pollen on Monarch Butterfly Larvae in Field Studies." *Proceedings of the National Academy of Sciences USA* 98(21):11931-11936.

Strauss, S.H. 2003. "Genetic Technologies: Genomics, Genetic Engineering, and Domestication of Crops." *Science* 300(5616):61-62.

Sung, D., F. Kaplan, K. Lee, and C. Guy. 2003. "Acquired Tolerance to Temperature Extremes." *Trends in Plant Science* 8(4):179-187.

Syngenta. 2002. *Syngenta Annual Report 2002*. Basel, Switzerland: Syngenta International AG.

Taylor, M.R., and J.S. Tick. 2003. "Post-market Oversight of Biotech Foods: Is the System Prepared?" Washington, DC: Pew Initiative on Food and Biotechnology. April 2003.

Tilman, D., K.G. Cassman, P.A. Matson, R. Naylor, and S. Polasky. 2002. "Agricultural Sustainability and Intensive Production Practices." *Nature* 418(6898):671-677.

Tucker, G. 2003. "Nutritional Enhancement of Plants." *Current Opinion in Biotechnology* 14(2):221-225.

[USDA NASS] U.S. Department of Agriculture, National Agricultural Statistics Service. 2004a. *Crop Production Acreage*. U.S. Department of Agriculture, National Agricultural Statistics Service. June 30, 2004. On-line at http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bba/

USDA NASS. 2004b. *Crop Production Annual Summary*. U.S. Department of Agriculture, National Agricultural Statistics Service. January 12, 2004. On-line at http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bban/

USDA NASS. 2004c. *Farm Numbers and Land in Farms*. U.S. Department of Agriculture, National Agricultural Statistics Service. February 27, 2004. On-line at http://usda.mannlib.cornell.edu/reports/nassr/other/zfl-bb/.

USDA NASS. 2003. *Farm Production Expenditures*. U.S. Department of Agriculture, National Agricultural Statistics Service. July 17,2003. On-line at http://usda.mannlib.cornell.edu/reports/nassr/price/zpe-bb/.

USDA NASS. 1997. *Trends in U.S. Agriculture: Price Index Ratio - Received to Paid: 1910–1997*. U.S. Department of Agriculture, National Agriculture Statistics Service. On-line at: http://www.usda.gov/nass/pubs/trends/pricesindex.csv.

Verrips, C., M. Warmoeskerken, and J. Post. 2001. "General Introduction to the Importance of Genomics in Food Biotechnology and Nutrition." *Current Opinion in Biotechnology* 12(5):483-487.

Welsh, R., B. Hubbell, and D.E. Ervin. "GM Crops and the Pesticide Paradigm." *Nature Biotechnology* 20:548.

Zhang, H.X., and E. Blumwald. 2001. "Transgenic Salt-Tolerant Tomato Plants Accumulate Salt in Foliage but not in Fruit." *Nature Biotechnology* 19(8):765-768.

Zhang. H.X., J.N. Hodson, J.P. Williams, and E. Blumwald. 2001. "Engineering salt-tolerant Brassica plants: Characterization of yield and seed oil quality in transgenic plants with increased vacuolar sodium accumulation" *Proceedings of the National Academy of Sciences USA* 98 (22): 12832-12836.

Zhu, J.K. 2001. "Plant Salt Tolerance." *Trends in Plant Science* 6(2):66-71.

Zhu, Y.L., E.A. Pilon-Smits, A.S. Tarun, S.U. Weber, L. Jouanin, and N. Terry. 1999. "Cadmium Tolerance and Accumulation in Indian Mustard is Enhanced by Overexpressing Gamma-glutamylcysteine Synthetase." *Plant Physiology* 121(4):1169–1178.

Zimmermann, M., and R. Hurrell. 2002. "Improving Iron, Zinc and Vitamin A Nutrition through Plant Biotechnology." *Current Opinion in Biotechnology* 13(2):142–145.

Zuo, J., Q. Niu, Y. Ikeda, and N. Chua. 2002. "Marker-Free Transformation: Increasing Transformation Frequency by the Use of Regeneration-Promoting Genes." *Current Opinion in Biotechnology* 13(2):173-180.

Zuo, J., Q.W. Niu, S.G. Moller, and N.H. Chua. 2001. "Chemical-Regulated, Site-Specific DNA Excision in Transgenic Plants." *Nature Biotechnology* 19(2):157–161.