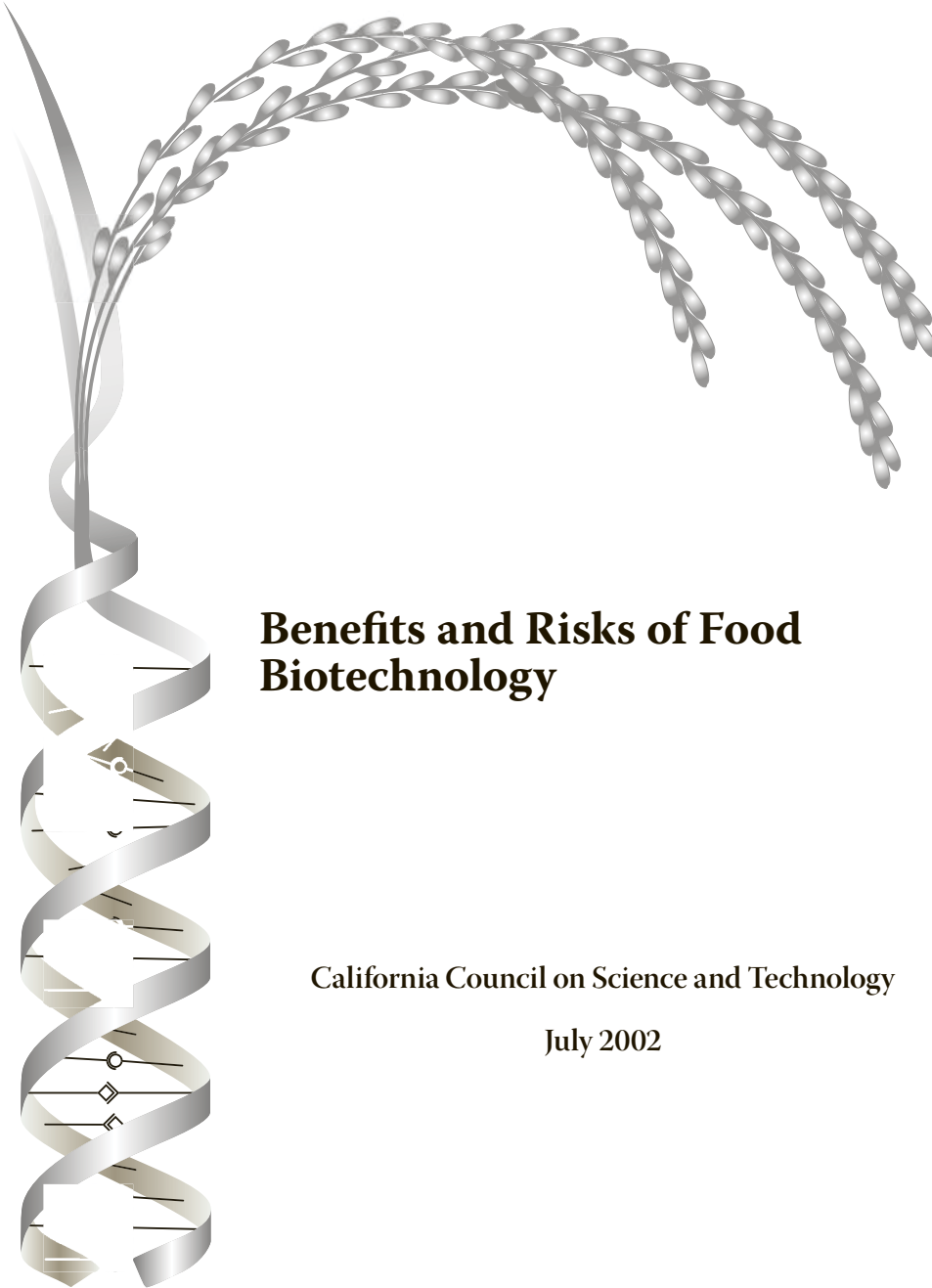




**Benefits and Risks of
Food Biotechnology**

June 2002

California Council on Science and Technology



Benefits and Risks of Food Biotechnology

California Council on Science and Technology

July 2002

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Table of Contents

PREFACE	1
EXECUTIVE SUMMARY	3
INTRODUCTION	17
CHAPTER 1: BIOTECHNOLOGY OVERVIEW, PRODUCT APPLICATIONS, CONSUMER RESPONSE BY CHRISTINE BRUHN	33
CHAPTER 2: SAFETY OF FOODS DERIVED FROM SPLICED-DNA CROPS BY GEORGE BRUENING	47
CHAPTER 3: TRANSGENIC CROP PLANTS AND THE ENVIRONMENT: BENEFITS AND RISKS BY NORMAN ELLSTRAND AND SUBRAY HEGDE	63
CHAPTER 4: SPLICED-DNA CROPS IN CALIFORNIA BY GEORGE BRUENING	83
CHAPTER 5: FEDERAL REGULATION AND POLICY ON TRANSGENIC PLANTS BY JOHN VANDERVEEN	99
CHAPTER 6: STATE REGULATIONS BY DAVE LUSCHER AND JOHN STEGGALL	121
CHAPTER 7: SCIENCE VERSUS PRESUMPTION IN ASSESSING RISK BY HENRY MILLER AND GREGORY CONKO	129
CHAPTER 8: BIOTECHNOLOGY AND INTELLECTUAL PROPERTY BY BRIAN WRIGHT	149
CHAPTER 9: A GUIDE TO NATIONAL AND INTERNATIONAL SCIENTIFIC REPORTS BY TAMARA SCHIOPU AND SEYMOUR VAN GUNDY	167
APPENDICES	
A: UC DIVISION OF AGRICULTURAL AND NATURAL RESOURCES STATEWIDE BIOTECHNOLOGY WORKGROUP WEBSITE (UCBIOTECH.ORG) LINKS TO WEBSITES	193
B: UC DIVISION OF AGRICULTURAL AND NATURAL RESOURCES STATEWIDE BIOTECHNOLOGY WORKGROUP WEBSITE (UCBIOTECH.ORG) GLOSSARY	201
C: PRINCIPAL AUTHORS	215
D: CCST ENVIRONMENTAL ISSUES COMMITTEE	223
E: REVIEWERS WHO PROVIDED WRITTEN COMMENTS	229
F: CALIFORNIA COUNCIL ON SCIENCE AND TECHNOLOGY	233

Tables and Figures

LIST OF TABLES

TABLE 1	
GLOBAL AREA OF TRANSGENIC CROP PLANTS GROWN FROM 1996 TO 2000 _____	31
TABLE 2	
THE TOP 20 CROPS GROWN IN CALIFORNIA AND THE UNITED STATES, AND THE TRANSGENIC CROPS NO LONGER REGULATION BY USDA _____	81
TABLE 3	
COMPARISON OF IMPROVED AND UNIMPROVED UPLAND AND PIMA COTTONS _____	93
TABLE 4	
ESTIMATES OF TRANSGENIC UPLAND COTTON ACREAGE IN CALIFORNIA _____	94
TABLE 5	
PERMIT REQUESTS FOR SPLICED-DNA FIELD TESTS IN CALIFORNIA _____	95
TABLE 6	
FOODS DERIVED FROM NEW PLANT VARIETIES DERIVED THROUGH RDNA TECHNOLOGY: FINAL CONSULTATIONS UNDER FDA'S 1992 POLICY _____	117
TABLE 7	
FOODS FROM NEW PLANT VARIETIES DERIVED THROUGH RDNA TECHNOLOGY: FINAL CONSULTATIONS UNDER FDA'S 1992 POLICY _____	119

LIST OF FIGURES

FIGURE 1	
WORLD PER CAPITA GRAIN PRODUCTION _____	26
FIGURE 2	
GLOBAL STATUS OF TRANSGENIC CROP COMMERCIALIZATION AND FIELD TESTING _____	32
FIGURE 3	
THE GLOBAL AREA OF TRANSGENIC CROPS FROM 1996 TO 2000 (MHA) IN THE INDUSTRIAL AND DEVELOPING COUNTRIES _____	32
FIGURE 4	
SAFETY ASSESSMENT OF NEW VARIETIES: SUMMARY _____	116

Preface From CCST Members

We are pleased to submit to the Food Biotechnology Taskforce our report on the Benefits and Risks of Food Biotechnology.

In September 2000, Senate Bill 2065 (authored by Senator Costa) was signed into law. SB 2065 voiced support for California's strong farm economy and its competitive edge in the world market for agricultural products. It also emphasized that recent advances in biotechnology made it desirable to inform consumers and reexamine the regulatory framework for this type of agricultural production.

SB 2065 created a Food Biotechnology Task Force (FBTF) to be co-chaired by the Secretary of the California Health and Welfare Agency, the Secretary of the California Technology, Trade and Commerce Agency, and the Secretary of the California Department of Food and Agriculture (CDFA). CDFA was designated the lead agency. The FBTF was requested to seek information from scientific and agricultural experts on the science and technology related to food biotechnology and to appoint an advisory committee consisting of representatives from consumer groups, environmental organizations, farmers, ranchers, representatives from the biotechnology industry, researchers, organic farmers, food processors, retailers and others with interests in the issues surrounding food biotechnology.

The FBTF subsequently contracted with the California Council on Science and Technology (CCST) to provide a preliminary report on current food biotechnology based on sound science and modern farming technologies. This report is intended to be a technical reference for the advisory committee and for the FBTF. It is not to be considered as the Task Force's final report under this legislation.

The FBTF was charged to evaluate the following: 1) definition and categorization of food biotechnology and production processes; 2) scientific literature on the subject and characterization of information resources readily available to consumers; 3) issues related to domestic and international marketing of biotechnology foods, such as handling, processing, manufacturing, distribution, labeling and marketing of these products; 4) potential benefits and impacts to human health, the state's economy, and the environment accruing from food biotechnology; and 5) existing federal and state evaluations and oversight procedures. The FBTF is requested to report on the issues studied, their findings, basis for the findings, and recommendations to the Governor and Legislature as further funding becomes available for this purpose.

In May 2001, CDFA provided CCST with a scope of work to prepare a "Preliminary Report Assessing the Science and Information on the Benefits and Risk of Food Biotechnology," referencing, detailing, and analyzing current scientific literature on genetically modified foods. As an independent body of scientific experts, CCST is well suited to respond to requests from the Legislature of this type.

CCST is an independent, not for profit organization established by state legislation in 1988 to actively represent the state's science and technology interests. Since its creation, the state's science and technology leaders from industry and academia have worked with state and federal agencies and government officials to recommend policies that will maintain California's technological leadership and a vigorous economy. CCST's recent reports and analyses have, for example, evaluated the state's science and technology infrastructure, reviewed public interest energy research programs, and proposed new methods for adopting electronic teaching materials in schools.

CCST was directed to select a balanced research team of principal authors comprised of academic and science policy experts with experience in one or more of the following disciplines: risk analysis, plant and animal biology, genetics, ecology, environmental science, ethics, agricultural and livestock economics, intellectual property protection, and public policy. The composition of the research team and the report outline was reviewed and approved by the FBTF, prior to initiation of the report. The biographies of the scientific team members are listed in Appendix C.

CCST has the highest principles in providing independent, objective, and respected work. All work that bears the Council's name is reviewed by Board Members, Council Members and Fellows. CCST also seeks peer review from outside experts. The process as well as the outcome is reviewed. This results in a protocol that ensures the issues are well addressed, the response is targeted and the results are clear and sound. The Environmental Issues Committee of CCST has overseen the production of this report. Biographies of committee members are included in Appendix D.

The FBTF requested that the scientific review report be written and presented in a manner that is most likely to be understood by the public and policy makers with no scientific background. The report has been peer-reviewed by a panel of experts convened by CCST and comprised of representatives from academia, industry and public interest. Principal investigators of the report were charged with the need to provide a scientific review, summary and critical evaluation of the status of food biotechnology literature with a California focus. They were asked to incorporate the concerns of public consumers, farmers (including the organic food industry), testing, regulation, labeling and handling in the market place, bio-safety, and food safety. The scope of the report was to include a review, summary and critical evaluation of the following topics, particularly as they relate to transgenic crops:

- Current definitions of food biotechnology and a categorization of production processes in use by regulatory, scientific and industry organizations.
- A brief summary of the current food biotechnology regulatory system in other countries, the U.S., California, and other states.

Existing research on the benefits and risks of food biotechnology, particularly as produced in California, as follows:

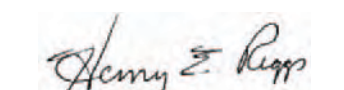
- Information related to safety and nutritional value of genetically modified foods;
- Known and potential negative or positive health effects on humans or animals;
- Findings on environmental impacts on water and soil quality, weeds, commercially related plants, domestic animals and other organisms, including fish;
- Known impacts on production and farming process, and on food processing;
- Known or potential ecological effects from cross breeding with related species, or on wildlife, pollination, and overall ecological systems;
- Economic or other benefits to consumers and to the food biotechnology industry; and
- Other (non-research) scientific reviews, analyses and surveys regarding potential impacts or benefits from food biotechnology, including impacts on commerce.

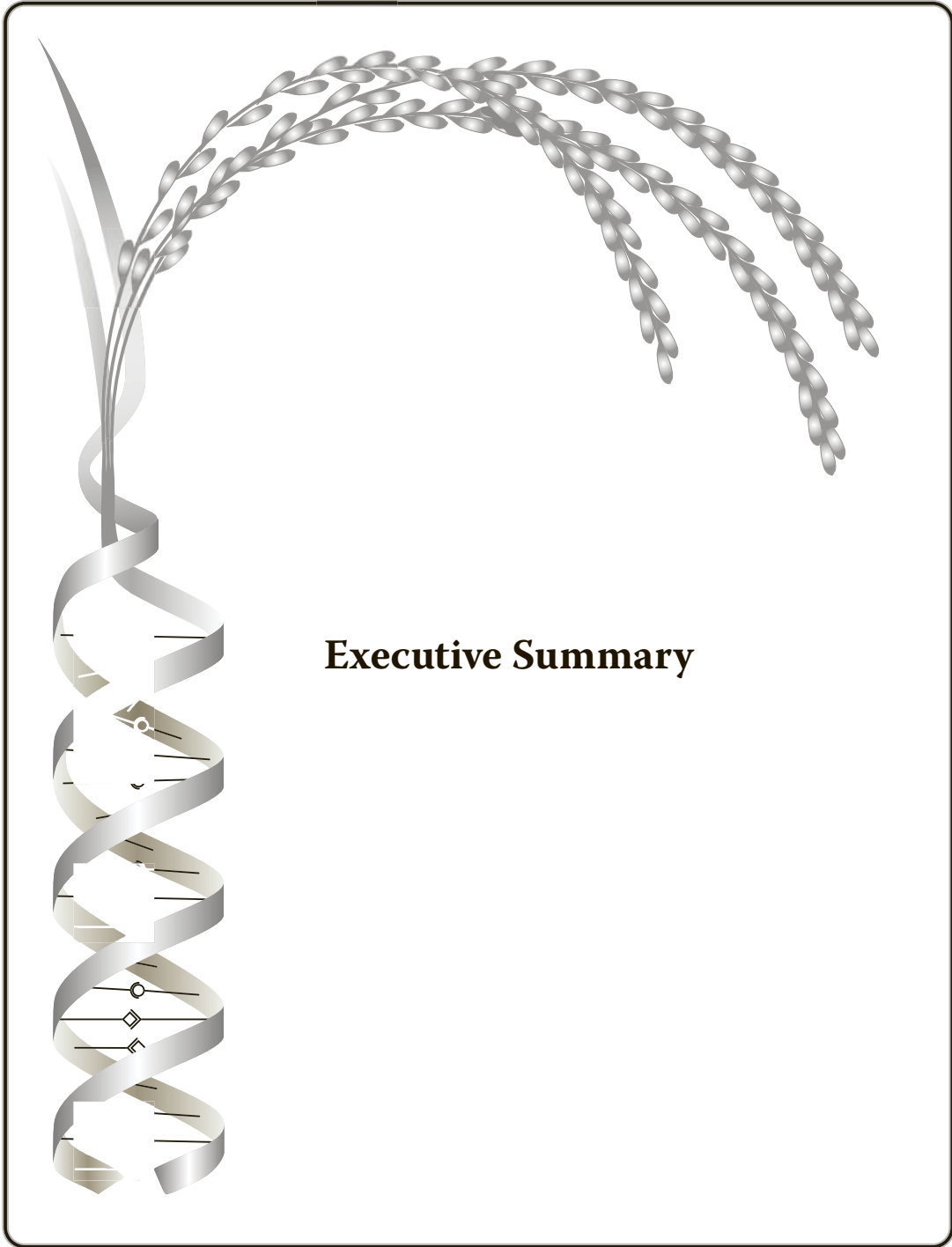
In addition to the scientific references quoted in this report, some additional selected scientific panel reviews are provided for the public and policy makers who would be interested in their conclusions and more detailed or specific information at their respective websites. The University of California Division of Agriculture and Natural Resources through its Statewide Biotechnology Workgroup provides a website, www.ucbiotech.org, with science-based information and databases for the public on issues relating to the application of biotechnology to crops. It has provided the glossary of terms and definitions along with a list of website links to information on biotechnology in the appendix of this report.

This report, while not claiming to be a comprehensive document, endeavors to provide current scientific knowledge regarding risks and benefits of food biotechnology that would be useful to the California public and policy makers.


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*Chairman, Environmental
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Executive Summary

Executive Summary

The objective of this report is to provide a concise review of the scientific literature on the benefits and risks of food biotechnology for the State of California Food Biotechnology Task Force and its Advisory Committee and is in response to California Senate Bill 2065 of 2000. The primary focus of this report is on crop biotechnology (the applications of biotechnology to agriculture) and any positive or negative impacts on human and animal feeding and the environment. Approximately 70% of the human food products in the marketplace contain some fraction of crops developed by the new biotechnology. However, approximately 75% of the U.S. corn and soybean crops, which are often planted to spliced-DNA lines, are consumed by farm animals.

Many definitions have been applied to the term “biotechnology.” A useful, broad definition – the application of biological systems and organisms to technical and industrial processes – encompasses a variety of old and new processes and products. The new biotechnology, a set of more precise enabling techniques for genetic analysis and modification at the molecular level, includes but is not limited to the precise cutting and joining of DNA to introduce new genetic constructions into organisms; synonyms include spliced-DNA technology, gene splicing or recombinant DNA (rDNA) technology.

The new biotechnology techniques offer a more versatile and precise method of introducing one or more genes (functional segments of DNA) into a plant from unrelated organisms than with traditional plant breeding or other forms of genetic modification such as radiation, embryo culture, and chemical mutation. In this report, we will use the terms “new biotechnology”, “spliced-DNA”, “rDNA”, and “transgenic” to avoid the confusion generated by “genetically modified organisms” (GMO), and genetic engineering. The Food and Drug Administration has discouraged the use of “GMO” because studies have indicated that consumer anxiety and misunderstanding increases whenever the word “genetic” is used.

Agricultural biotechnology of the last two decades has shown promising benefits for increasing food and fiber production for a burgeoning world population, reducing pesticide pollution, improving food quality, and providing new pharmaceuticals and bio-fuels for the future. Agricultural biotechnology is a genetic modification tool used to customize plants with special qualities that can allow farmers to grow crops that are more nutritious, more resistant to pests and diseases, and more productive. There are many types of genetic modification that do not involve spliced-DNA technology.

In the future, new crop plants may be the source of valued medicines, biochemicals, chemical feedstocks, and specialty “niche” crops.

Current and Near-market Benefits of New Biotechnology Products on the Market	
Primary Benefits	Secondary Benefits
<ul style="list-style-type: none"> ● Plant resistance against insects ● Herbicide tolerance ● Plant resistance against pathogens ● Reduced pesticide use ● Higher crop yields ● More nutritious composition of foods ● Improved taste and quality 	<ul style="list-style-type: none"> ● Improved pest and weed management ● Improved soil conservation and reduced acreage requirements ● Reduced water and soil contamination by pesticides ● Reduced input agriculture ● Preservation of natural resources ● Expanded crop gene pool

The introduction of any new technology brings not only benefits but also risks, both real and imagined. Spliced-DNA crop technology has raised potential questions regarding food safety risks, environmental risks, and other social and ethical issues for the consumer. Two facts about spliced-DNA crops have fueled the debate about their regulation and acceptance. First, the source of the introduced DNA may be taxonomically distant from the plant species, e.g., from a bacterium. Second, current technology does not control the location in the genome at which the new, DNA-spliced transgene is introduced. However, discussions and debates about the possible consequences of large scale production of spliced-DNA crops and the consumption of spliced-DNA foods often have been based on unsupported suppositions as well as facts with the worst case scenarios based primarily on suppositions. The ethical principles and goals that should be considered in this debate are: ensure that all stakeholders are heard; maintain a safe, nutritious, and plentiful food supply; preserve ecosystems; and balance agricultural production and wise stewardship of the earth.

Potential Benefits and Risks	
Potential Benefits Expected in the Near Future	Potential Risks
<ul style="list-style-type: none"> ● Reduced fertilizer use ● Reduced levels of natural toxins in plants ● Reduced crop/food spoilage ● Simpler and faster methods to monitor for pathogens, toxins, and contaminants in foods ● Improved animal feeds 	<ul style="list-style-type: none"> ● New food allergies ● Antibiotic resistance transfer ● Pollen contamination/gene flow ● Decreased genetic diversity ● Development of insect resistance ● Development of weed resistance ● Development of virus resistance/new viruses ● Increased naturally occurring toxins ● Crossing species boundaries ● Effects on non-target organisms ● Long-term effects ● Social effects of new technology
Potential Benefits Expected Further Down the Road	
<ul style="list-style-type: none"> ● Plant-produced pharmaceuticals & vaccines ● Reduction of allergenic proteins; enhanced protein quality ● Turning plants into biosensor for hazardous materials ● Tolerance to drought and floods ● Tolerance to salt and metals ● Tolerance to heat and cold ● Save plants threatened by extinction 	

Many critics of spliced-DNA technology believe that the economic benefits of spliced-DNA crops have not been distributed equitably. Although scientific data are sparse and just being developed for pest resistance and herbicide resistance varieties, the early indications suggest that U.S. farmers are currently receiving the greatest economic benefits of pest-resistant *Bacillus Thuringiensis* (*Bt*) cotton and herbicide-tolerant soybeans (42% to 72%). U.S. consumers appear to receive the least benefits from these crops, 7% and 4% of the total, respectively. Monsanto Company, one of the pioneering firms in the applications development of spliced-DNA crops, and other seed companies received most of the remaining economic benefits.

Probably the most striking effect of these crops is the reduction in pesticide applications (15 million fewer applications for cotton and 19 million for soybeans per year). In the case of *Bt* cotton, growers were able to reduce insecticide applications by 2.7 million pounds in 1999. The value of currently available traits conferred by spliced-DNA genes, depends in a given growing season, on the degree of pest or weed infestation. The new spliced-DNA “agronomic” traits lend reliability to crop production by being available from the planted seed, with little additional effort and reduced requirements for surveillance and reduced attention to application methods and timing. Reliability in production and reduced pesticide usage are of value to the consumer even if the benefits are not obvious in food prices. Future spliced-DNA genes conferring quality traits rather than agronomic traits likely will provide improved food quality and other benefits more obvious to the consumer.

The 19th century efforts in crop genetic improvement, in the form of sexual crosses, including crosses between species, and selection for improved traits, preceded the establishment of genetics as a science. More aggressive manipulations of plant genes in the 20th century took the form of mutations induced by radiation or chemicals and development of plant organ and tissue culture techniques, all preceding the first laboratory experiments in spliced-DNA, transgenic plants in 1983. The field test of new biotechnology plants took place in 1987 and the first commercial field test was in 1992. The first commercial production was in 1996 after the safety studies were completed in 1995. Currently, there are 53 transgenic crop varieties that have been deregulated for commercial production in the United States. Research and testing is being conducted on dozens of plant species, and commercial scale production of gene-spliced crops including soybean, corn, canola, cotton, potato, squash, and papaya is underway. The global acreage of these crops has increased from 4.3 million acres in 1996 to almost 110 million acres in 2000 in 13 countries on all six continents. Field-testing of new transgenic crops continues in both developed and developing regions of the world.

Though the production of transgenic crops is growing in developing countries, transgenic plants should not be regarded as magic bullets that will eliminate poverty and hunger, because these global problems have significant political and social components that influence the availability of food even where food can be grown in sufficient amounts. However, all approaches to crop improvement must be considered in order to improve the efficiency of agriculture and thereby minimize human suffering and reduce the ecological impacts of a global population expected to increase by 50% during the first half of the 21st century.

Compared to the major field crop agriculture of the U.S. Midwest and South, California’s highly diverse agriculture has had only limited experience with transgenic crops, mainly cotton. California is the nation’s primary producer of health-benefiting foods in the form of fresh fruits and vegetables. In contrast to the agronomic spliced-DNA-conferring traits that are prominent in today’s field crops, California’s crop agriculture could benefit from improved quality traits such as enhanced vitamin, flavanoid or mineral content, and better flavor and texture. However, agronomic traits such as herbicide tolerance, salt tolerance, and drought resistance also could be of value in a variety of California crops. Many new crops (approximately 30 varieties) have been developed by the new biotechnology in California’s research laboratories and are being field tested; however, the costs of registration and concerns regarding food processor and consumer acceptance have delayed their entry into the market place.

The health of farm animals may also be improved through biotechnology by developing crops that are more easily digested by animals, and by reducing the phosphorous, nitrogen, and odor of animal waste. Transgenic crops and their products have been grown and marketed extensively since 1996 without any reported ill effects on human and animal health.

In this report, we present an overview of the current thinking on the new biotechnology. Although referencing national and international studies, we are particularly concerned with the impact and

importance of the new biotechnology to Californians. A synopsis of the following nine chapters prepared by scientists in their fields of specialty is provided to summarize the balance of the report. The scientists who have contributed to this report are all currently involved with assessing the opportunities and concerns of the new biotechnology at the state, national, and international level.

Chapter 1, Biotechnology Overview, Product Applications Consumer Response by Christine Bruhn, Director, Center for Consumer Research, University of California, Davis.

This chapter presents a general overview of biotechnology, food biotechnology, a discussion of benefits and risks, product applications, and consumer attitudes.

In a consumer survey conducted in 2001, only about 36% of the U.S. consumers were aware that genetically engineered products were in the marketplace even though as much as 70% of the processed foods they were eating could contain some ingredients that originated from transgenic crops. On the other hand, as many as 70% of the consumers indicated that they would purchase produce modified by biotechnology to reduce pesticide use, 66% would purchase produce modified to contain more vitamins and nutrients, and 58% would purchase products modified for better taste. In conclusion, 64% of the consumers surveyed value the benefits of genetic engineering and have confidence in scientific innovation that will bring benefits in the next five years.

Chapter 1: Biotechnology Overview	
Food Applications-Potential Benefits	Areas of Concern-Potential Risks
<ul style="list-style-type: none"> ● Increased crop yield ● Improved nutrition ● Reduced allergenicity ● Medical benefits ● Healthier farm animals ● Environmental benefits ● Aids in food processing 	<ul style="list-style-type: none"> ● Agribusiness consolidation and competition ● Allergenicity ● Antibiotic resistance transfer ● Contamination of organic crops ● Decreased genetic diversity ● Environmental balance ● Herbicide resistance ● L-Tryptophan ● Naturally occurring toxicants ● Pest resistance ● Virus resistance

Chapter 2, Safety of Foods Derived from Genetically Modified Crops by George Bruening, Professor of Plant Pathology and Director, Center for Engineering Plants for Resistance Against Pathogens, University of California, Davis.

This chapter covers the food safety perspective from the viewpoint of postulated general risks, comparison of outcomes from conventional and spliced-DNA gene transfer, food labeling and the “precautionary principle.” Those who are concerned with possible effects of spliced-DNA crops appear to accept two hypotheses on implicit benefits or implicit risks.

The scientific issue is whether transgenic crop products are quantitatively different from crops resulting from non-spliced-DNA technologies. Each hypothesis is discussed regarding the location and degree of expression of a transgene, the antibiotic gene, and proteins and allergens. Nutritional benefits discussed include the changing of the oil content mixture in soybeans to produce high-performance cooking oils and reduced saturated fats to improve cholesterol nutrition of humans. “Golden Rice®” varieties have been developed to increase the beta-carotene content, a precursor of Vitamin A, and iron for eliminating a severe nutritional deficiency in children in rice-consuming cultures. Although increased allergenicity in crops is still a major concern and risk to food safety and labeling issues, it is pointed out that the techniques of genetic engineering have and can be used to reduce allergens in foods as they have done experimentally in rice, wheat and other foods. European regulators have invoked a “precautionary principle” as part of their official regulatory framework for transgenic crops and crop products but not for conventionally developed crops and crop products. Essentially, this principle requires the technique to be absolutely safe. Since this is a standard unattainable by human endeavor, political judgment may be substituted for scientific analysis.

Chapter 2: Food Safety	
Benefit Hypotheses	Risk Hypotheses
<ul style="list-style-type: none"> ● Research to date together with the history of safe usage of the transgenic proteins in agriculture and/or their similarity to already occurring constituents provide a substantial assurance of safety of our foods. 	<ul style="list-style-type: none"> ● A gene, gene fragment or other DNA sequence from a taxonomically distance source, introduced into an uncontrolled location in the plant genome, results in a greater risk than a DNA sequence from a closely related source introduced by a conventional genetic cross or DNA sequences modified by other conventional techniques. ● Adverse effects may appear only years or decades after widespread deployment of spliced-DNA sequences in crop plants, because current testing of spliced-DNA crops will likely fail to detect problems not currently recognized or problems that may appear later due to postulated variability, instability or delayed effects associated with spliced-DNA crops.

Chapter 3, Transgenic Crop Plants and the Environment: Benefits and Risks by Norman C. Ellstrand, Professor of Genetics and Subray Hegde, Research Geneticist, University of California, Riverside.

This chapter points out that technological innovations bring their own set of benefits and risks to the environment. No technology is 100% safe. This is true for transgenic crop plants that contain novel traits incorporated by the tools of biotechnology. The available information suggests that transgenic crops may hold both promise and peril for the environment depending upon a variety of factors including the type of transgenic crops grown under cultivation, the nature of the transgenic traits involved, and the geographic location of crops in relation to wild relatives.

The most important criterion in the risk-benefit analysis of the impacts of transgenic crop plants on the environment is that the risks or benefits should be compared to conventional agricultural practices. Detection of slow and cumulative negative impacts of transgenic crops on the environment is harder to measure relative to immediate benefits. Since these transgenic crops have been grown commercially for such a short period of time, it is difficult to know the full extent of these risks. So far, there is no evidence that transgenic crops harm the environment any more than traditional agriculture; however, without systematic monitoring, the lack of evidence of damage is not necessarily a lack of damage.

Chapter 3: Transgenic Crop Plants	
Potential Environmental Benefits	Potential Environmental Risks
<ul style="list-style-type: none"> ● Indirect environmental/economic benefits for higher crop yields ● Reduced chemical toxicity in the environment due to pest-resistant cultivars ● Efficient use of renewable resources such as land, water, and soil nutrients ● Accurate monitoring of environmental pollution using pollution-sensitive transgenic plants 	<ul style="list-style-type: none"> ● Movement of transgene itself with subsequent expression in a different organism or species ● Direct or indirect risks with whole transgenic plants ● Non-target risks associated with the transgene product outside the plant ● Risks associated with increased use of herbicides ● Risks associated with the resistance evolution in pest populations

Chapter 4, Spliced-DNA Crops in California by George Bruening, Professor of Plant Pathology and Director, Center for Engineering Plants for Resistance Against Pathogens, University of California, Davis.

A revolution in crop agriculture since 1996 has resulted in substantial penetration of spliced-DNA cultivars into U.S. plantings of cotton, soybean, and corn. California has generally been a leader in agricultural innovation but only spliced-DNA cotton has seen significant production in California.

The high costs of research and of satisfying regulatory requirements meant that the first implementations of spliced-DNA crops were with crops having very large-scale plantings. In 2001, transgenic cotton accounted for 36% of California's cotton acreage. The author points out that the intense genetic manipulation to which cotton has been subjected, represents what has occurred in major crops in general and serves as an illustrative example of the benefits and risks. Transgenic cotton grown in California contains transgenic traits for herbicide resistance (bromoxynil and glyphosate), insect resistance (*Bt*) and stacked transgenes for both herbicide and insect resistance. The benefits of herbicide-tolerant cotton have been documented at a savings of \$150 per acre. In addition to improving yield and quality of cotton, the use of these varieties allows for better conservation tillage and narrow row spacing for more plants per acre. Synthetic insecticide applications have been reduced to levels not seen since the 1940s. New pest-resistance cultivars might lead to efficient crop cultivation where pest pressure previously made production impossible. This could be especially important to crop production in rapidly urbanizing California and in developing countries.

There are concerns about the level of the regulatory processes and protocols used to instill public faith in the safety of spliced-DNA crops. A recent 2002 report from the National Academy of Sciences,

Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation, called for an enhanced regulatory process by soliciting greater public input and more scientific peer review. In the United States, there are three federal government agencies that have primary responsibility for regulating bioengineered foods: the Food and Drug Administration, the Department of Agriculture, and the Environmental Protection Agency. Many critics believe that the lack of coordination between the three agencies has led to regulatory inconsistency, regulatory scrutiny not commensurate with risk, lack of risk balancing, excessive paper work, and excessive costs of testing and registration. Therefore, three sections of this report have been devoted to the regulatory policy and process for registration of transgenic plants.

Chapter 4: California Situation	
<ul style="list-style-type: none"> ● California produces over 350 different agricultural crops and has the largest food and agricultural economy in the nation with a gross cash income for 1999 of \$26.7 billion. ● It is the nation's leader in agricultural exports shipping over \$6 billion in both food and agricultural commodities around the world. ● Its agricultural industry generates more than \$70 billion in related economic activity for the state. ● California has been a leader in the technology and development of new and improved crops through its agricultural research in both the public and private sectors. ● California is headquarters for the global biotechnology industry. 	
Potential Benefits	Potential Risks
<ul style="list-style-type: none"> ● The most extensive commercial transgenic crop produced in California is cotton, its second largest cash crop, and it remains important for both domestic use and for export. ● The potential for California to gain economic benefits comparable to those seen for the major field crops. 	<ul style="list-style-type: none"> ● The costs of registration, a major financial hurdle for most small acreage specialty crops which are a substantial portion of California's 350 different crops. ● The future public acceptance of about 30 crop species that have been the subject of field testing permit requests for spliced-DNA crops in California still remains uncertain. ● Ability of California to remain competitive in the global agricultural economy of the 21st century.

Chapter 5, Federal Regulations and Policy on Transgenic Plants by John E. Vanderveen, Emeritus Scientist of the Center for Food Safety and Applied Nutrition, Food and Drug Administration.

As discussed in this chapter, the federal government has in place a broad and comprehensive approach for policy formation and regulation of developing and using recombinant DNA (rDNA) biotechnology derived foods as mandated by federal law. In the United States, there are three federal agencies that have had primary responsibility for regulating bioengineered foods and have maintained an active process for setting policy on bioengineered foods since the 1980s. They are the Food and

Drug Administration, the United States Department of Agriculture (USDA), and the Environmental Protection Agency (EPA).

Traditional regulatory approaches for many classes of new products have focused on an evaluation that considers both the magnitude and likelihood of plausible health or environmental harms on one hand and the expected benefits on the other hand. For transgenic crops, the highly risk-averse approach to regulation has taken the “precautionary principle.” The idea of this principle is that governments should implement regulatory measures to prevent or restrict actions that raise even conjectural threats of harm to human health or the environment as long as there is incomplete scientific evidence as to the potential significance of these dangers. An analysis of food safety in 2000 by the Institute of Food Technologists stated unequivocally that the theoretical considerations and empirical data do not support more stringent safety standards for biotechnology products than those that apply to conventional foods. Dozens of new plant varieties produced through conventional breeding and genetic modification techniques other than genetic engineering enter the marketplace and food supply every year without any scientific review or special labeling. Currently, the paperwork and field trial testing required by the USDA for gene-spliced organisms is 10-20 times more expensive than the virtually identical organisms that have been modified with conventional genetic techniques.

The challenge for regulators is to balance all the competing factors in a way that reduces overall harm to public health. It is important that regulators take into consideration the ambient level of restraint generally imposed by society on individuals’ and companies’ freedom to perform legitimate activities such as scientific research.

Chapter 5: National and International Regulatory Systems

- Regulations of bioengineered foods are divided into four main areas:
 - Safety of cultivation and environment
 - Plant incorporated protectants
 - Safety regulation of rDNA biotechnology derived foods
 - International harmonization and trade
- The Food and Drug Administration (FDA) has broad authority to regulate all foods that are derived from new biotechnology food crops.
- The USDA Animal and Plant Health Inspection Services (APHIS) is responsible for protecting the environment from pest and disease, field testing, and commercial sale of agricultural bioengineered plants.
- The EPA is responsible for registering plant incorporated protectants, setting environmental tolerances, and establishing exemptions in and on crops.
- The USDA Economic Research Service conducts research on the economic impact of the production of rDNA biotechnology-derived crops.
- Other federal agencies have roles relating to policy development, international harmonization, research, and information.
- The United Nations' Food and Agricultural Organization (FAO), World Health Organization (WHO), United Nations Environmental Program (UNEP) is the focus of most of the international agreements and standards. The major international activity concerning standards for foods derived from rDNA is centered in the committees of the joint FAO/WHO Codex Alimentarius Commission (CAC).
- The World Trade Organization (WTO) is the authoritative scientific body to be used in trade disputes.
- The Organization for Economic Cooperation & Development (OECD) assists in fostering marketing systems and building strong economics in developing countries.

Chapter 6, State Regulations by Dave Luscher, Senior Agricultural Biologist and John Steggall, Senior Environmental Research Scientist, Pesticide Management, California Department of Food and Agriculture.

The authors of this chapter describe how California, like most states, has deferred to the federal government for regulation of biotechnology products. The California Department of Food and Agriculture (CDFA) reviews and provides comments to the United States Department of Agriculture (USDA) on forward applications for federal permits to bring new spliced-DNA organisms or crops into the state for research purposes. Currently, CDFA does not have the in-house technical expertise to do an in-depth critique of the genetic engineering methods and of the special environmental hazards.

Chapter 6: State Regulatory Control

- In 1985, a state task force was formed to review state and federal regulations regarding new biotechnology. The task force recommended that no special state regulations were justified for genetically engineered products.
- In 1994, a task force subcommittee recommended against specific labeling for biotechnology derived foods. Thus, food derived from genetically engineered sources is regulated in California under the same rules that govern conventional food industries. Some state agencies do request and review technical information regarding genetic modifications for research and experimental use permits.

Chapter 7, Science versus Presumption in Assessing Risk by Henry Miller, Research Fellow, Hoover Institution, Stanford University and Gregory Conko, Policy Analyst and Director of Food Safety Policy, Competitive Enterprise Institute, Washington, D.C.

The authors of this chapter suggest that the current federal regulatory policies on the testing and commercialization of plants and foods developed with the techniques of the new biotechnology make neither scientific nor common sense.

“Biotechnology” is a continuum of techniques for genetic improvement of plants and other organisms. There is long-standing scientific consensus that: the newer molecular techniques for genetic improvement are an extension, or refinement, of earlier, far less precise ones; adding genes to plants or microorganisms does not necessarily make them less safe either to the environment or to eat. The risks associated with gene-spliced organisms are the same in kind as those associated with conventionally modified organisms and unmodified ones; regulation should be based upon the risk-related characteristics of individual products, regardless of the techniques used in their development. There is no scientific rationale for additional regulatory requirements for the products of gene-splicing.

Dozens of new plant varieties produced through hybridization and other traditional methods of genetic improvement enter the marketplace and food supply each year – without any scientific review or special labeling. Many such products are from “wide cross” hybridizations in which large numbers of genes – including even entire chromosomes or whole genomes – are moved from one species or one genus to another and incorporated randomly into the host genome, yielding a plant variety that does not and cannot exist in nature. These new varieties of plants, obtained by pre-gene-splicing techniques – which are “genetically engineered” or “genetically modified” by any reasonable definition – have long been consumed widely and routinely in the United States, Europe and elsewhere; they include wheat, corn, rice, oat, tomato, potato, rice, pumpkin, and black currant. In order to reduce risks most effectively, the degree of regulatory scrutiny applied to individual products should be commensurate with the degree and type of risk being addressed.

Chapter 7: Governmental Regulation of Spliced-DNA Foods	
Potential Benefits	Potential Risks
<ul style="list-style-type: none"> ● Balanced sound policy ● Safety for farmers ● Safety for food producers ● Safety and assurance for consumers ● Safety in the environment ● Registration of new biotechnology products; foods, drugs, vaccines, and diagnostic tests 	<ul style="list-style-type: none"> ● Imposes unscientific, excessive regulatory requirements ● Uses highly risk-averse approach to regulation ● Uses “acceptable levels” that may not be biologically realistic ● Subjects DNA-modified organisms to lengthily, mandatory pre-market review ● Fosters inconsistent approach to the introduction of new plant varieties ● Inflates the costs of research and development ● Diverts and wastes public- and private-sector resources ● Shrinks the numbers and kinds of products under development ● Inhibits the development of environment-friendly products ● Deprives consumers of choices in the marketplace

Chapter 8, Biotechnology and Intellectual Property by Brian Wright, Professor of Agricultural Economics, University of California, Berkeley.

In this chapter, the author deals with intellectual property right (IPR) issues. In recent years, patents have become an important means of protecting innovations by crop breeders and producers of related technologies. Patents have furnished strong investment incentives. But, the author argues that the number of patents relevant to particular lines of research is increasing rapidly, and overlapping, uncertain, and conflicting claims threaten the freedom of researchers to operate. In the private sector, one response has been mergers and takeovers to eliminate the need for costly and difficult negotiation of licensing transactions. But, the public-sector breeder is still crucial for most California crops, and means must be formed to give them adequate freedom to operate in producing new cultivars for California’s farmers. In general, changes in biotechnology and intellectual property protection are mutually reinforcing.

The scope and power of IPRs in biotechnology has grown, its international reach has expanded, and the innovative response has been impressive. The Plant Variety Protection Act of 1970 administered by the USDA gives some protection to new distinct varieties against unauthorized sale for replanting and places restrictions on replanting saved seed by producers. Enforcement, however, has been difficult except in the case of hybrid seeds that will not breed true when replanted. Historically, the dominant player in producing new crop varieties has been the public sector. Starting in the 1980s, biotech companies formulated a strategy of selling crop protection traits. In response to high transaction costs and other difficulties with licensing patents, the first wave of integration of agricultural chemical, biotech companies, and seed companies created major life science companies such as Monsanto and

Novartis. Now the industry is moving toward mergers that could integrate the input and output side of agriculture driven largely by attempts to get around further contracting problems associated with IPRs for new biotechnologies, and to obtain the benefits of greater market power.

Implications of these mergers for California producers depend upon the focus of the private-sector investment in agricultural research, now match or exceed the public investment in research. To date, the bulk of private investment has focused on a small number of high-value crops, mainly corn, soybeans, and cotton that represent large markets. California's main crops have not been the prime targets of genetic engineering efforts by large agricultural biotechnology companies. Thus, if the development of new biotech crops for California's agriculture is left to the private sector, many applications of biotechnology to California crops are likely to be delayed or blocked altogether. Collaboration between producer groups and public-sector universities and public institutes is one promising way of bringing biotechnology to California's specialty crops. Policymakers should try to ensure that nonprofit researchers have access to the necessary enabling technology on reasonable terms.

Chapter 8: Intellectual Property Rights	
Potential Benefits	Potential Risks
<ul style="list-style-type: none"> ● Provides strong incentives to agricultural research ● Provides legal protection for biological innovations ● Encourages private-sector investment in agriculture ● Makes private crop research attractive for the first time in non-hybrid crops ● Biotech research gives value to intellectual property rights (IPRs) in agriculture ● Research organizations, both public and nonprofit, are able to capture more of the value generated by biotech research than just giving it away for free 	<ul style="list-style-type: none"> ● Favors well-financed private research conglomerates ● Limits or blocks some collaborative private and public research efforts ● Limits freedom to operate in agricultural research ● Promotes proliferation of conflicting proprietary rights ● Limits research access by national and international research centers ● Difficult to enforce infringement, protection, and legal challenges ● Need for development of alternative forms of technology transfer

Chapter 9, A Guide to Current National and International Scientific Reports by Tamara Schiopu, MBA Candidate in Environmental Management and Seymour Van Gundy, Emeritus Dean and Professor of Nematology, University of California, Riverside.

In this chapter, the authors provide an introduction and a brief summary of the many national and international scientific reviews conducted since 1999.

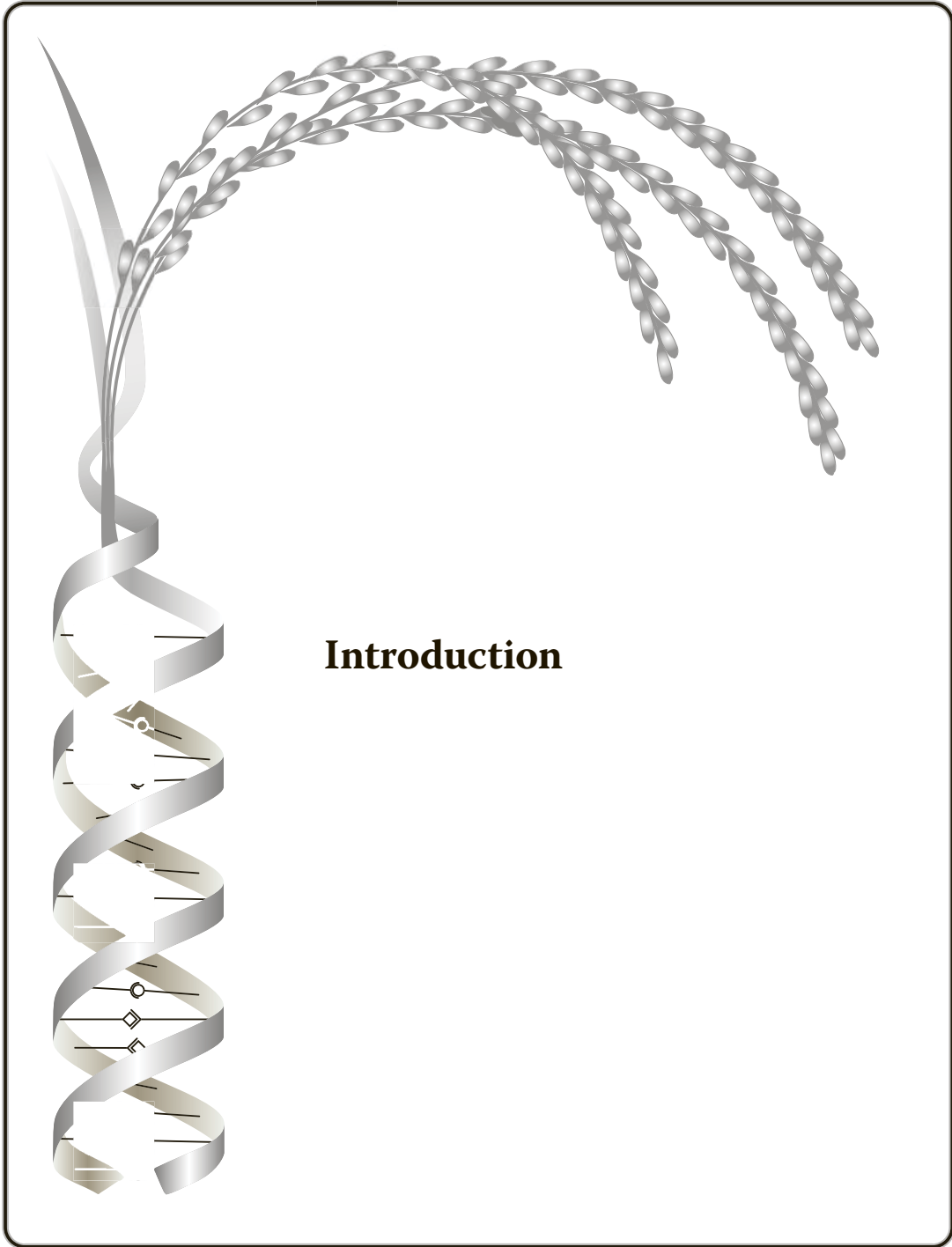
The controversy and debate on food biotechnology and the development of transgenic crops is global in nature and extends from the scientific community to the farmer and the public consumer with the eventual resolution of policy and regulation in the hands of governmental agencies and politicians. The Internet has become the primary means of information exchange and provides an instant communication on the benefits and risks of transgenic crops by all the scientific organizations, governmental agencies, public consumer organizations, and individuals that want to make their reports,

views, and opinions known to the world. For example, a search on any commercial search engine will provide more than 79,900 citations. Unfortunately, there is no Internet screen to identify those that report information based on scientific data.

Obviously, an extensive review of all the information available on transgenic crops is beyond the scope, timeframe, and resources of this review. Only summaries and recommendations of the most important recent scientific reports are presented for comparison and extension of some subject areas not covered in the body of the report. The full reports are readily available to the consumers as downloads on the Internet. Additional web-links are available in the appendix. The subject of food biotechnology has been reviewed by many national and international scientific panels in the last two years and there is now extensive literature available in this report for those who want to develop a meaningful understanding and dialog that is based on sound science.

Chapter 9: Scientific Reports

Many scientific organizations who have endorsed the safety and benefits of new biotechnology and transgenic crops include the U.S. National Academy of Sciences, Genetics Society of America, American Medical Association, and American Dietetic Association and internationally the World Health Organization, Food and Agricultural Organization of the United Nations, The Royal Society of United Kingdom, and Third World Academy of Sciences.



Introduction

Introduction

George Bruening, University of California, Davis and

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In this Introduction, we set out (i) to describe, briefly, the new crop improvement technology of DNA splicing, first commercialized in 1994, (ii) to compare the new technology with prior approaches to crop genetic improvement, (iii) to assess likely general outcomes from the planting of spliced-DNA crops, and (iv) to report on the current status of spliced-DNA crop plantings, animals, economics, and ethics.

DNA SPLICING IN CROP IMPROVEMENT

In the 1860s, the Austrian monastery abbot Gregor Mendel showed that inheritance of characters in pea plants occurs under the control of units known as genes. However, long before Mendel, from prehistoric times, farmers were genetically improving crop plants by selection. Crop improvement was placed on a scientific basis and accelerated in the 20th century with the rediscovery of Mendel's laws, the application of statistics and other mathematical tools to plant breeding, and the ability to induce mutations and select valued crop traits from mutated populations and genetic crosses. The latest revolution in crop improvement can be traced to the discovery in the 1940s of deoxyribonucleic acid (DNA) as the chemical substance of genes. James Watson's and Francis Crick's 1953 finding of the double-stranded and symmetrical structure of DNA provided immediate insight into how this molecule can encode genetic information and can provide the blueprint under which each organism operates. DNA has four chemical units or "nucleotides," designated A, C, G, and T. Each organism receives its blueprint of DNA, with its specific order of A, C, G, and T nucleotides, from its parents (or parent). It is the order of these nucleotides in the very long DNA molecules of each chromosome that specifies the genes. It is single genes, and more often combinations of genes, that result in traits of the organism, whether it is an animal, a plant or a microorganism. Each cell of an

organism interprets the order of nucleotides by the same code, a genetic code. The genetic code varies only slightly from organism to organism. The biochemical mechanisms that allow genes to confer traits, usually involving the synthesis of a functional protein, and are very similar in different organisms. Thus, at the molecular level, the biosphere of planet Earth has a single biology.

Proteins that provide the same function in two different organisms often are very similar, and the genes that encode the corresponding proteins therefore are similar. Mere inspection of the sequence of nucleotides that encode a protein usually does not reveal whether the protein is from a human, a fish, a tomato, or even a bacterium. The distinctiveness of an organism is the result of its entire set of genes and the interacting controls that determine, as influenced by the organism's environment, the time and extent to which each gene is expressed.

By the 1970s, DNA-splicing technology allowed researchers to isolate specific genes and to create many additional copies of the gene by transfer to the common laboratory bacterium *Escherichia coli*. To imagine how this process works in a more familiar context, consider DNA as the biological equivalent of a video recording tape. Like videotape, DNA carries information that can be transcribed, multiply copied, and even cut out and spliced into a new location. A modified videotape with information rearranged from the original or a tape with a segment of another tape spliced in would be called the recombinant videotape. A videotape player translates information from electromagnetic signals into pictures and sounds. Similarly, the cell's machinery translates the DNA nucleotide sequences, by means of another information molecule ribonucleic acid (RNA), into proteins that direct the cell's functions and determine many of its characteristics.

The technology of DNA splicing allows the precise cutting and joining of DNA molecules regardless of their source to create new DNA molecules in the laboratory. DNA-splicing technology was brought to crop improvement in 1983 when DNA splicing was combined with microbiological tools for introducing DNA into the existing gene set (the "genome") of single plant cells. Most plant transformation today uses one of two approaches for introducing the DNA: bombardment with free DNA on particles or T-DNA in bacteria. In the free-DNA method, DNA carrying the gene of interest is coated on microscopic metal particles that are accelerated by compressed gas or explosive charge and driven into cells in culture or cells near the surface of plant tissue. In the T-DNA method, a non-pathogenic version of the plant pathogenic bacterium *Agrobacterium tumefaciens*, bearing the DNA of interest, introduces the desired genes into the plant cell chromosome. Both methods allow a defined DNA sequence to be transferred, but the location in the plant genome occupied by the new gene is not controlled. The number of copies of the new DNA generally can be controlled better using *Agrobacterium* than by using particle bombardment.

The result using either method of DNA introduction is a "genetically transformed" cell. Plant tissue culture methods developed in the 1950s and 1960s allowed an intact, fertile plant to be regenerated from the single cell. Every cell of the new plant, including the precursors of the pollen and egg cells, will have the DNA blueprint of the initial, single cell. If that initial cell bears spliced-DNA introduced by the transformation technology, the new plant will have the inserted DNA in every cell. Therefore, many of the progeny of the plant regenerated from the transformed single cell also will bear the introduced DNA segment.

As is indicated above, neither the site of insertion of the defined DNA segment in the genome or the number of copies inserted is controlled by present plant transformation technology. Additionally, the process of regeneration may introduce apparent abnormalities, most of which disappear after passage through a sexual generation. However,

some genuine mutations also may result from the process of regeneration, introducing occasional changes in the DNA of the plant in addition to the inserted sequence.

A typical recommendation for a model plant system is that 20 plants be selected from the progeny of a single transformation and regeneration experiment in order to be assured of obtaining progeny lines with a desired set of characters. Each plant is derived from a separate transformation event and therefore has the spliced-DNA inserted at a different site(s) in the plant DNA and perhaps with different truncations or random alterations of the inserted sequence. Some spliced-DNA inserts produce the same unintended effects in many of the progeny lines, suggesting that the unintended effect is the result of the product of the spliced-DNA insert; that is, a high frequency of a specific unintended effect suggests a metabolic alteration due to a spliced-DNA gene product rather than a transformation-event-specific or site-of-insertion-specific alteration. Unintended effects occur among plant lines derived from conventional breeding as well as among lines derived by transformation and regeneration, and the described selection process from many progeny is applied in both conventional and spliced-DNA breeding.^{1,2}

For crop plants, typically hundreds of transformed plants will be tested. Among the tested transformed lines, there usually will be several having the new DNA inserted at a single site and showing all measured characteristics identical to those of the original cultivar except for those characteristics attributable to the newly introduced DNA sequence. That is, it usually is possible to select from the transformed plants a number of lines that bear the introduced spliced-DNA nucleotide sequence as a new, Mendelian gene. Often the crop plant line that is suitable for

¹ Dunsmuir, P., Bond, D., Lee, K., Gidoni, D. & Townsend, J. (1987). Stability of introduced genes and stability of expression. In *Plant Molecular Biology Manual C1*, pp. 1-17. Edited by S. B. Gelvin, Schilperoort & D. P. S. Verma. Dordrecht, Belgium: Kluwer Academic Publishers.

² Kuiper, H. A., Kleter, G. A., Noteborn, H. P. J. M. & Kok, E. J. (2001). Assessment of the food safety issues related to genetically modified foods. *Plant Journal* 27, 503-528.

transformation and regeneration is not a desired elite cultivar, and extensive conventional crossing is required to transfer the new Mendelian gene into an elite cultivar.^{3,4,5}

Spliced-DNA crops are biotechnology products. However, spliced-DNA is only one aspect of biotechnology, which is a broader category. It is convenient to recognize a subset of biotechnologies, those dedicated to the precise analysis or alteration of DNA nucleotide sequences and designated here as “new biotechnology.” We relate DNA splicing to the two broader categories in a three-tier definition:

- Biotechnology: The application of biological systems and organisms in technical and industrial processes intended to create products and services;
- “New Biotechnology”: a set of techniques enabling gene analysis and modification at single-nucleotide resolution; and
- This includes, but is not limited to, the precise cutting and joining of DNA to introduce new genetic constructions into organisms (“DNA splicing” or “recombinant DNA”).

COMPARISON OF CROP GENETIC IMPROVEMENT TECHNOLOGIES

Humans have selected and modified plants and animals since the beginning of civilization. The history of cultivated wheat illustrates how breeding and natural selection have produced the products we use today. The seeds of wild wheat disperse when their brittle seed heads shatter. Presumably in the early stages of domestication, perhaps 10,000 years ago, natural variation (mutations) occurred and some wheat produced seeds that shattered only at a low frequency in the field. Seeds from

³ Dunsmuir, 1987.

⁴ Benedict, J. H. & Altman, D. W. (2001). Chapter 8. Commercialization of transgenic cotton expressing insecticidal crystal protein. In *Genetic Improvement of Cotton. Emerging Technologies*, pp. 137-201. Edited by J. N. Jenkins & S. Saha. Enfield, New Hampshire: Science Publishers, Inc.

⁵ Perlak, F. J., Oppenhuizen, M., Gustafson, K., Voth, R., Sivasupramaniam, S., Heering, D., Carey, B., Ihrig, R. A. & Roberts, J. K. (2001). Development and commercial use of Bollgard(R) cotton in the USA: Early promises versus today's reality. *Plant Journal* 27, 489-501.

non-shattering seed heads were easier to gather than those which scattered on the ground. Without human intervention, this mutated wheat probably would not reproduce successfully. Because of easy gathering, wheat with this characteristic would have become widely planted by early humans. Over the years, people selected varieties with other improved characteristics, such as greater yield, shorter growth cycle, and quality characteristics of the crop product, such as durum wheat for making pasta and hard and soft wheat for use in various baked products.

Field corn, sweet corn, Indian corn, and pop corn all were derived by natural variation from teosinte, the ancestor of modern corn. This plant, found in Mexico, contains a few hard seed kernels on grass-like stalks. The evolution of teosinte into corn, with its very different appearing architecture, including heavy ears on short stalks, apparently required relatively few gene changes, so that teosinte and corn are considered to be subspecies of the same *Zea mays* species. Similarly, humans selected desirable characteristics in domestic animals and developed specific breeds seen today in dogs, cats, cattle, horses, chickens, and other animals.

A DNA nucleotide is the unit of genetic information. The order, i.e., the “sequence,” of A, C, G, and T nucleotides determines the instructive power of genes in facilitating the developmental and functional capabilities of the organism. Genetic improvement of crops depends on taking advantage of changes in nucleotide sequences, the order of A, C, G, and T nucleotides, whether by mutations that change the sequences locally or by rearrangements of DNA that create new juxtapositions of sequences. The processes of crop domestication selected naturally occurring DNA sequences that conferred traits deemed favorable by ancient farmers. Accidental genetic crosses also contributed to the development of crop plant lines with improved traits, and purposeful genetic crosses have been carried out since the 19th century. Plant breeding was placed on a scientific basis by the rediscovery of Mendel's research in the early 20th century. The engine of crop genetic improvement is genetic variation, because genetic variation is the input from which plant breeders derive desired traits. Naturally occurring radiation and mutagenic chemicals, as well as transposons and other “mobile” DNA elements of the plant genome,

all contribute to altering nucleotide sequences in plants and to creating new juxtapositions of DNA sequences. A number of technologies, derived before DNA splicing, have been developed in the past 70 years, both to increase genetic variability and to facilitate moving genes between plants. Described here are induced mutations, wide genetic crosses, and protoplast fusions.

Induced Mutations

In the 1930s, L.J. Stadler used radiation to induce mutations in plants, thereby increasing the genetic variation available from which to select lines showing valued traits. The use of chemically induced mutations followed. Even in the era of DNA splicing, the technology of induced mutations is advancing and cultivars continually are being derived from lines bearing induced mutations.⁶ There are now over 2,200 cultivars with inputs from induced mutations, compared to about 1,700 in 1998⁷ and 30 in 1964 when the International Atomic Energy Agency began to promote mutagenesis technology. Banana, barley, grapefruit, ornamentals, rice, and wheat are representative of the crop and crop groups improved by induced mutations.

Wide Genetic Crosses

A species generally is defined as the group of individuals for which sexual crosses can occur under usual field conditions. Greater genetic variation becomes available if genetic crosses are not limited to the single species. Mechanical transfer of pollen from a potential male parent from one species to a selected potential female parent from another species usually will not result in seed formation. About 100 years ago, progeny were obtained from artificial crosses between some species closely related to, in fact in the same genus as, wheat.⁸ Occasionally crosses between species from closely related genera were also accomplished. These are examples of “interspecific” crosses because the genes from two distinct species were combined in the progeny. In

⁶ Maluszynski, M. (2001). Officially released mutant varieties: The FAO/IAEA database. *Plant Cell Tissue and Organ Culture* 65, 175-177.

⁷ van Harten, A. M. (1998). *Mutation Breeding: Theory and Practical Applications*, pp. 353. Cambridge, U.K.: Cambridge University Press.

⁸ Fedak, G. (1999). Molecular aids for integration of alien chromatin through wide crosses. *Genome* 42, 584-591.

the 1930s, plant tissue culture methods allowed plant geneticists to create other wide, “interspecific” crosses that otherwise could not be accomplished because of recognition by the parent of foreign material in the developing embryo or seed. The new ovule rescue or embryo rescue technology extended the number of species pairs that yield viable progeny but still required that the parental species be closely related, in the same or closely related, genera. The grain triticale, a wheat-rye hybrid first produced in Germany in the 19th century and re-created in the 1970s, is an example of a new species generated from an intergeneric cross.⁹ More typically in a wide cross, a wild relative of a crop plant is crossed to the crop plant with the intent of introducing valuable traits that are not available in cultivar lines. Consider an example from tomato breeding. *Lycopersicon peruvianum* is a wild tomato that is genetically highly polymorphic and therefore a valued source of new genes for the cultivated tomato *Lycopersicon esculentum*.^{10, 11} The intervention of embryo rescue provided a successful cross of *L. esculentum* and *L. peruvianum* at UC Davis.¹² This cross and similar crosses introduced nematode resistance and virus resistance traits that still are in use in tomato culture.

Protoplast Fusion

The fusion of protoplasts (cells from which the cell wall was removed) may be performed with two species from the same genus or even from two closely related genera. If the two parental lines are sufficiently compatible, fertile plants may result after plant regeneration. Protoplast fusion, like a wide genetic cross, combines DNA sequences derived from the entire genomes of the parental lines in an uncontrolled fashion. Subsequent loss of genetic material generates a new stable line, designated in a

⁹ Villareal, R. L., Varughese, G. & Abdalla, O. S. (1990). *Advances in Spring Triticale Breeding*.

¹⁰ Rick, C. M. (1963). Barriers to interbreeding in *Lycopersicon peruvianum*. *Evolution* 17, 216-232.

¹¹ Sacks, E. J., Gerhardt, L. M., Graham, E. B., Jacobs, J., Thorup, T. A. & St Clair, D. A. (1997). Variation among 41 genotypes of tomato (*Lycopersicon esculentum* Mill.) for crossability to *L. peruvianum* (L.) Mill. *Annals of Botany* (London) 80, 469-477.

¹² Smith, P. G. (1944). Embryo culture of a tomato species hybrid. *Proceedings of the American Society for Horticultural Science* 44, 413-416.

protoplast fusion experiment as a “somatic hybrid.” Although the first plant somatic hybrid was created in 1972, applications to crop improvement have been limited. Protoplast fusions have resulted in hibiscus with more showy flowers, transfer of a cytoplasmic male-sterile trait from radish to cabbage, and *Solanum* (potato) species with improved vigor. Both wide crosses and protoplast fusion are capable of generating a new plant species.

All crop genetic improvement, even selection on random variation and selection out of crosses between lines of the same species, results in changes in DNA nucleotide sequences. Induced mutations, wide genetic crosses, protoplast fusion, and, of course, DNA splicing coupled to plant transformation and regeneration, all change nucleotide sequences and bring into juxtaposition sequences that normally would not be present in the same cell. Although some cultivars, particularly of vegetatively propagated woody species, have been derived directly by selection of one member from a large cultivar population treated with ionizing radiation, the progeny lines derived after inducing mutations or performing wide genetic crosses often are not useful directly as a cultivar. Usually, many traits other than the desired new trait(s) will have been altered in plant lines derived from mutagenesis, wide cross, or protoplast fusion. Plants must be crossed again and again (backcross series) to a desired cultivar (the recurrent parent) to breed out undesirable characteristics while retaining the traits of interest.

As described in the previous section, both conventional and spliced-DNA breeding produce variants among the progeny from which lines with desired properties are selected. In comparison to the progeny of a conventional cross, a line selected after transformation and regeneration of a cultivar is likely to be closer to being a cultivar, or to being the parent of a cultivar in the case of crops sold as hybrid seed. DNA splicing provides versatility and precision. Any DNA compatible with the recipient plant line can be introduced without introducing other significant changes in the genome. In contrast, a wide genetic cross may introduce, from the wild plant parent, an undesired gene encoding an allergen or an enzyme catalyzing a reaction leading to an unfavorable flavor component, or it may confer some other undesired

trait. Similarly, induced mutations also may result in an unsuspected metabolic change.

IS SPLICED-DNA TECHNOLOGY A GOOD OPTION FOR CROP IMPROVEMENT?

In the context of meeting the needs of California, the United States, and the world, a logical equivalent of the above question is “Are conventional, non-DNA-splicing approaches to crop improvement, alone, likely to provide a better outcome under any reasonable set of scenarios than a combination of DNA-splicing and conventional approaches?” Although there has been significant deployment of transgenic crops in many areas of the world, opposition to spliced-DNA crop technology remains, based on concerns about possible adverse unintended effects and, in some cases, the possibility of gaining trade or other economic advantage from excluding or demonizing food products from spliced-DNA crops. Those who believe that the introduction of spliced-DNA crops presents significant risk, and that such risk is unacceptable, contend that the abundance and low cost of food in the more developed regions of the world makes application of DNA splicing to crop improvement unnecessary. They hold that where food is not as readily available, the cause lies more in poverty, poor distribution, and armed strife than in insufficient food production, and therefore DNA-spliced crops will not significantly help people in the less developed parts of the world. Some prominent scientists from less developed countries^{13, 14} point out that improving local food production through the application of spliced-DNA crops can overcome limitations of poverty and poor food distribution.

Regulators of the European Community propounded a *de facto* three-year moratorium on new approvals of spliced-DNA foods and invoke the “precautionary principle” as part of their official

¹³ Pearce, F. & Wambugu, F. (2000). Feeding Africa. *New Scientist* 166, 40-43.

¹⁴ Wambugu, F. (1999). Why Africa needs agricultural biotech. *Nature* 400, 15-16.

regulatory framework.^{15,16} The European Commission legislation specifically excludes traditional methods for genetic crop improvement from regulation and focuses on DNA splicing. In contrast, U.S. Food and Drug Administration officials stated that the risk from DNA splicing to be no greater than the risks associated with other methods for crop improvement.¹⁷

“FDA has not considered the methods used in the development of a new plant variety (such as hybridization, chemical or radiation-induced mutagenesis, protoplast fusion, embryo rescue, somaclonal variation, or any other method) to be material information within the meaning of section 201(n) of the act {21 USC 321(n)}”

The stated principle logically should have directed U.S. policies that treated cultivars derived from spliced-DNA technology and conventional technology identically. However, in practice, only spliced-DNA cultivars have been subjected to regulation in the United States. The Canadian Food Inspection Agency, in contrast, defines “plants with novel traits” (PNTs) to include plant lines derived by conventional means and treats them identically with regard to the requirements for confined field trials and approval for commercial release.¹⁸

“PNTs may include plants derived using recombinant DNA technology or traditional plant breeding techniques, including mutagenesis, somaclonal variation, or wide crosses. Novel traits are those that when introduced into a specific plant species, result in a novel plant that may be considered unfamiliar, when compared with plants of the same species already on the market and may not be considered substantially equivalent to similar, familiar plant types already in use and regarded as safe.”

For those who find DNA-splicing technology to be as benign as, or more benign than some other crop plant technologies, choosing not to use the best available technology, including spliced-DNA technology, is contrary to the goals of minimizing the environmental intrusion that agriculture inevitably brings.

RECOGNITION IN CALIFORNIA OF SPLICED-DNA CROPS AND FOODS

In California, 1984 Resolution 170 authorized California to become the first state to develop a biotechnology policy. In 1985, The Assembly Office of Research prepared a report “Biotechnology: A Regulatory Review” in which it recommended the formation of the “California Interagency Task Force on Biotechnology.” The Task Force was chaired by the state’s Trade and Commerce Agency which served as a liaison for Task Force members who represented Food and Agriculture, Health Services, Fish and Game, Office of Environmental Health Hazard Assessment, Pesticide Regulation, Consumer Affairs, Industrial Relations and Water Resources Control Board. In its 1986 report,¹⁹ the Task Force addressed public health and safety issues, permit system for testing, and approval of spliced-DNA products, and it reviewed the adequacy of state and federal statutes for regulating products derived from biotechnology. It set the stage for the regulatory process for approval of spliced-DNA products in California. The issue

¹⁵ Council of the European Communities (1990). Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms. Community legislation in force, *Biotechnology: A Regulatory Review*, Prepared by the Office of Research, April 1985.

¹⁶ European Commission (2000). Communication from the European Commission on the Precautionary Principle, pp. 29. Brussels: Commission of European Communities.

¹⁷ FDA (1992). Food and Drug Administration. Statement of policy: foods derived from new plant varieties. Federal Register 57, 22984-23001 (<http://vm.cfsan.fda.gov/~lrd/biotechm.html>).

¹⁸ Regulatory Directive 2000-07: Guidelines for the Environmental Release of Plants with Novel Traits within Confined Field Trials in Canada <http://www.inspection.gc.ca/english/plaveg/pbo/dir/dir0007e.shtml>. 2000, Canadian Food Inspection Agency. Plant Health and Production Division, Plant Biosafety Office: Ottawa, Ontario, Canada.

¹⁹ Biotechnology – California Permits and Regulations. September 1986. Prepared by the California Interagency Task Force on Biotechnology. 212 pp. Document 390L0220. http://europa.eu.int/eur-lex/en/lif/dat/1990/en_390L0220.html. Official Journal L, European Economic Community 117, 0015-0027.

of labeling of spliced-DNA foods and related safety issues was addressed later in a 1994 report²⁰ by a subcommittee of the California Interagency Task Force on Biotechnology. In summary, the consensus of the subcommittee concluded that it was unnecessary to require special labeling of foods derived from biotechnology, as a class, because such labeling would provide no protective or material health and safety information. They stated:

“Foods derived from new plant varieties developed through genetic engineering – have not been associated with, or identified as introducing, new or inherently different, food safety hazards than those posed by foods developed through traditional plant breeding methods.”

As with traditionally developed plant foods, determinations of labeling requirements for biotech foods must be made on an individual basis. When a potential health risk occurs, the consumer needs to be informed through special labeling. In 1996, the California Research Bureau prepared at the request of Assemblyman John Vasconcellos an extensive update on the “Bioindustry: A Description of California’s Bioindustry and Summary of the Public Issues Affecting Its Development.”²¹ This report appeared after three years of industry-sponsored field testing and just prior to large scale commercial production of spliced-DNA field crops.

In 1998, the California Research Bureau prepared a report “Inventing Biological Organisms: A Reader of Selected Articles”²² addressing three fundamental issues: the ethics of patenting human DNA, biological organisms, or their parts; how individual, community, multinational, and natural ownership of human DNA and organisms affects the development of biotechnology; and the economic advantages and disadvantages of patenting.

²⁰ Food Labeling Subcommittee Report, 1994, prepared by the Food Labeling Subcommittee of the California Interagency Task Force on Biotechnology, 31 pp and Appendix I-IV.

²¹ Koehler, Gus A. 1996. Bioindustry: A Description of California’s Bioindustry and Summary of the Public Issues Affecting Its Development. California Research Bureau, 93 pp. www.library.ca.gov/html/statseg2a.cfm.

In support of California’s strong farm economy and its competitive edge in the world market for agricultural products, in light of recent advances in spliced-DNA crops, because of the need for informing consumer and in its interest in understanding the regulatory framework, the California Legislature authorized an update on the state of food biotechnology by Senate Resolution No. 34 and Senate Bill 2065, creating a Food Biotechnology Task Force.

GLOBAL FACTORS INFLUENCING ADOPTION OF SPLICE-DNA CROPS

On a global scale, the factors affecting the demand for greater efficiency in food production, and for higher quality food, include human population growth, rising expectations and income, diminishing habitats for non-human species, diminishing agricultural inputs such as water, topsoil and petroleum, potential effects of global climate changes and other not readily controllable events, and possible future need to obtain energy and chemical feedstocks from crops, for example as ethanol or biodiesel fuel and bioplastics.

Projections by the United Nations Population Division place likely upper and lower bounds on world population over the next half century.²³ The world’s population was estimated at 6.2 billion at the end of 2001. For most human populations, replacement is achieved at 2.1 children per woman, which corresponds to the average fertility for the more developed regions of the world. Under the implausibly optimistic assumption that world birthrates fall to replacement, rather than the three births for each death that is the average in less developed regions, world population will level out in 2050 at 7.8 billion. Stabilization of the human population would require 50 years because the average age in less developed regions is 24 years, versus 37 years in more developed

²² Koehler, Gus. 1998. Inventing Biological Organisms: A Reader of Selected Articles. California Research Bureau, 10 pp. www.library.ca.gov/html/statseg2a.cfm.

²³ Chamie, J. (2001). World Population Prospects. The 2000 Revision. Highlights. www.un.org/esa/population/unpop.htm, pp. 34. New York: United Nations Population Division.

regions. An assumption that current fertility does not decrease provides an upper bound of 13 billion people in 2050, with the earth's population still rising. The world's population currently is growing at a rate of 1.2% per year, and fertility is declining, though the decline is less rapid than it was in the mid 1990s. Probably it is not realistic to expect the world's population to grow by less than about half, to 9.3 billion, in 2050, the equivalent of a compounded rate of 0.83% per year. Even under the middle scenario, the absolute growth in world

grain production provides animal feed. According to United Nations Food and Agriculture Organization figures, grain yield per hectare harvested increased in the last 40 years of the 20th century at a compounded average of rate of just over 2% per year, based in significant part on conventional, non-DNA-splicing, crop improvement. The result was a significant reduction in the proportion of the world's people at risk of starvation, to 600-800 million at the end of the 20th century, an increase in the proportion of human diet calories derived from meat, and a decline

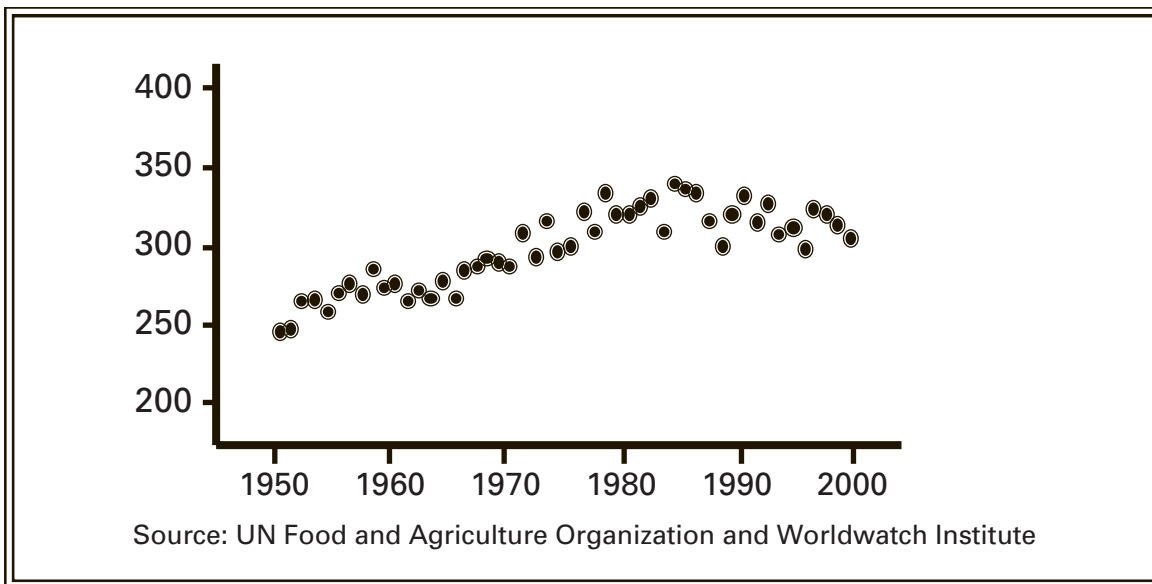


Figure 1: World per capita grain production²⁴

population in the next 25 years will approach the growth for the last quarter of the 20th century. United Nations population analyses take into account the projected effects of AIDS and some continuing armed conflicts.

Considering the data in Figure 1, in order for food production to keep pace with population growth, the minimum annual increase must be 0.8% to 1.2%. Grain production is a good proxy for total food production, since grain is the principal food for most of the world's people and about a third of

in grain prices, corrected for inflation. Therefore, extrapolation into the 21st century of 20th century yield gains would suggest, by a comfortable margin of error, an abundance of food even if the total area of plowed land remained constant. The optimism of this extrapolation must be tempered with consideration of the technical requirements for continued grain yield increases and of changing global conditions.

Crop genetics has increased yields primarily by raising the productive stand density and the harvest index, with lesser contributions from greater crop plant resistance against pathogens and pests. The efficiency of conversion of sunlight into photosynthate has remained nearly unchanged. Plants growing at a high density in the field effectively can use more water and fertilizer per unit of land area. Short stature plants can have a larger proportion of captured photosynthate in the grain,

²⁴ Food & Agriculture Organization (2000). Conference 5. Can agricultural biotechnology help to reduce hunger and increase food security in developing countries? Electronic forum on biotechnology in food and agriculture. www.fao.org/biotech/logs/C5/summary.htm: United Nations Food and Agriculture Organization.

rather than elsewhere in the plant (improved harvest index). The record high yield of corn in the USA in 1938 corresponds to the average corn yield in the late 20th century, about 135 bushels per acre (about 8.6 t/ha). The current yield record is about 400 bushels per acre, and 500 bushels per acre record yields have been predicted. Record yields are achieved at very high planting densities in favorable soils prepared and planted very carefully year after year. The methods for achieving record yields are generally known but have not been achieved generally, and the percentage annual increase in yield for corn and other grain has fallen steadily. Indeed, grain yield increase increments have been constant or slightly reduced in recent years. On a per capita basis, grain production averaged over the world actually has fallen slightly since 1985 (Figure 1).

The decline in per capita grain production sometimes has been cited as supporting the need for improved crop productivity through use of spliced-DNA-derived traits. However, the decline probably cannot be attributed to an inability of grain production to keep pace with population growth, because there is little evidence for the increases in real grain prices that might signal significant real per capita grain production deficits. Reduced production probably reflects reduced demand in Asian markets, the release of grain from inventories, and the end of, or great reductions in, subsidies on grain production for animal feed that were formerly in place in the planned economies of eastern European countries.²⁵ Some forecasts by agricultural economists anticipate rising grain prices over the next few decades; other forecasts indicate falling grain prices.

Factors not directly related to crop genetic improvement but affecting grain production and utilization include increased incomes and rising expectations likely to increase the demand for meat. Slightly less than two kg of grain protein can be converted to a kg of poultry meat protein under the most favorable conditions. Conversion rates for hogs, feedlot cattle and dairy cattle are in the range of 6-10 kg of grain protein per kg of meat or milk protein. Grain and other crop products converted to fuel or chemical

feedstocks possibly will further reduce grain available for food. Losses of land to urbanization and erosion²⁶ also affect crop production. High agricultural yields also rely on irrigation in many areas of the world. The area of irrigated agricultural grew faster than the world's population for most of the 20th century, but since 1980, the area of irrigated land per capita has declined. In only about 25 years, 30% of the world's population is expected to live in countries that have severe agricultural water scarcity.²⁷ Under current production methods, nitrogen fertilizer is essential to high grain yields. However, if natural gas prices rise, nitrogen fertilizer prices will rise because natural gas is the source of energy and hydrogen for ammonia synthesis. Natural gas availability is uncertain because reserves, although apparently great, are difficult to document.

The uncertainties about future food production, and issues of food security in general, favor applying new methods for improving food production and quality, providing that the risks associated with the new methods are not significantly greater, and preferably less, than the risks associated with current technology. Realities of competition in an era of facile world trade mean that adoption of spliced-DNA crops in one area may place farmers who use cultivars improved only by conventional means at a disadvantage, enhancing the tendency to adopt the newer technology. As is reported in the next part of this Introduction, transgenic field crops now are widely planted in the United States and elsewhere, employing genes that confer insect resistance and weed control capabilities not available from conventional breeding.

In summary, world food needs likely could be met through the middle of the 21st century, assuming the middle projection of population growth, without resort to DNA-spliced crops. However, this prediction is uncertain, and increased food production requires greater inputs of land, water (particularly irrigation

²⁵ Johnson, D.G. (1999). The growth of demand will limit output growth for food over the next quarter century. Proceedings of the National Academy of Sciences for the United States of America 96, 5915-5920.

²⁶ Pimentel, D. (2000). Soil erosion and the threat to food security and the environment. *Ecosystem Health* 6, 221-226.

²⁷ Seckler, D., Amarasinghe, U., David, M., de Silva, R. & Barker, R. (1998). World water demand and supply, 1990 to 2025: Scenarios and issues. Research Report 19. <http://www.cgiar.org/iwmi/pubs/pub019/RR019.htm>. Colombo, Sri Lanka: International Water Management Institute.

water), minerals and fossil fuel energy, all very likely to increase environmental degradation. The lack of any demonstrated greater adverse effect, or of any scientifically supportable prediction of future adverse effect, from the introduction of spliced-DNA crops compared to conventionally bred crops, coupled with the ability of these crops to increase food security and to reduce the net intrusion of agriculture into the environment, provides a logic to the adoption of spliced-DNA crops along with other research-based technological improvements. Additionally, the realities of competition in an era of facile world trade mean that adoption of spliced-DNA crops in one area of the world may place farmers elsewhere who use only cultivars improved by conventional means at a disadvantage, enhancing the tendency to adopt the newer technology.

ANIMAL BIOTECHNOLOGY, OTHER ORGANISMS, AND LIVESTOCK FEEDS

Animal Biotechnology

The first transgenic mouse was produced in 1981 and they are now used regularly to produce monoclonal antibodies and anti-inflammatory agents, products with potential use in treating infection and diseases. Since then sheep, cows, and pigs have been cloned; however, cloning of animals does not involve spliced-DNA technology. In the future, spliced-DNA maybe used in combination with cloning to produce rejection free animal-to-human transplants. Currently, there are no animals produced by the new biotechnology that are approved for human consumption by the FDA. The most prominent research on genetic modification of animals is aimed at producing proteins, human enzymes, and the production of tissues and organs in animals for medical uses. A recombinant form, rBST, of the natural hormone, bovine somatotropin, is used to increase milk production. It is used to treat over 30% of U.S. cows. The development of transgenic aquatic organisms, such as shrimp and fish are under investigation in many laboratories and their release in California is under consideration by the Legislature. Another example of potential non-plant genetic engineering is the potential modification of insects for control of plant, animal, and human diseases.

Other Organisms

Several genetically modified bacteria and fungi are commonly used in food production. They are grown in vats and the enzymes extracted from them are used in a wide array of food and industrial applications, the most common food item being Chymosin which is used in the making of 60% of the hard cheeses. The production of antibiotics by organisms has been enhanced by one form or another of genetic modification to increase antibiotic production. The subject of genetic modification of micro-organisms has already been covered in the report by Koehler, 1998.

Livestock Feeds

As much as 75% of U.S. corn and soybean crops each year, much of which comes from spliced-DNA lines, are eaten by animals. Smaller quantities of canola, cottonseed, and potato are also fed to animals. The safety of livestock food as with human foods in the U.S. is regulated by the FDA. In addition to the regular safety assessment of feedstocks, there are assessments of the consumption of the animal product by consumers, worker safety and any other environmental aspects from the use of the feed. Feedstock-related benefits of biotechnology include:

- Improved protein quality by balancing amino acids to reduce nitrogen in waste;
- Reduced environmental impact of phytate in animal waste; and
- High oil corn that results in high energy density, resulting in more meat per ton of feed.

The Ag Biosafety Education Center at the University of Nebraska²⁸ concluded that the protein and DNA contained in foods and feeds, whether obtained from non-GM or GM crops, were typically degraded upon consumption by the normal digestive processes. For commercially available GM crops that are components of livestock feeds, there was no evidence of significantly altered nutritional composition, deleterious effects, or the occurrence of transgenic DNA or proteins in subsequent foods of animal origin. Scientific data, together with

²⁸ Higley, Leon G, et al. 2001. Food Safety Assessment. University of Nebraska Ag Biosafety Education Center. <http://agbiosafety.unl.edu/about.htm>.

the history of safe usage of transgenic proteins in agriculture and/or their similarity to already occurring constituents, provide a substantial assurance of safety of feedstocks.

ECONOMIC BENEFITS OF TRANSGENIC CROPS IN THE U.S.

Benefit Estimates

The new biotechnology crops currently being grown feature resistance to pests and the ability to tolerate herbicides. By 2000, roughly one-fifth of the U.S. corn acreage, over half the soybean acreage and almost three-quarters of the cotton acreage were planted to these new transgenic varieties. Updated crop benefits are presented from a 2001 report.²⁹ In the case of insect-resistant *Bt* corn varieties, the control was aimed at the control of the European Corn Borer, an insect that is difficult to control by conventional insecticides and by biological control. Consequently, growers were reluctant to use insecticide sprays and therefore took an estimated loss of 300 million bushels of corn per year. Thus, the primary benefit of *Bt* corn were increases of 66 million bushels in 1999, the equivalent of production on nearly 500,000 acres. Only modest reductions in insecticides have taken place since the introduction of *Bt* corn. In the case of cotton, both insect and herbicide-resistant varieties have been adopted widely. Insects (tobacco budworm, cotton bollworm, and pink bollworm) have been a major production problem because the management of these pests required several insecticide treatments per year along with the development of insecticide resistant insect populations. With the introduction of *Bt* cotton, it is estimated that cotton growers reduced insecticide use by 2.7 million lbs and reduced the number of insecticide applications by 15 million per year in 1999. At the same time, cotton production increased by 260 million pounds with net revenues increasing by \$99 million. With the introduction of herbicide-resistant cotton, there was a reduction of 19 million herbicide applications in 2000. In the case of herbicide tolerant soybeans, growers were able to reduce the number of herbicide applications by 19 million in 1999 and a cost reduction in weed control

of \$216 million. Although there were no significant increases in yields over conventionally grown soybeans, the changes in herbicide mix allowed farmers to control weeds without the application of herbicides that harm rotation crops thus improving the flexibility of soybean crop rotations. With the rapid adoption by farmers and continued development of new biotechnology crops, it is likely that the economic and agronomic impacts will be more evident as the technology evolves.

Distribution of Benefits

This new agricultural biotechnology, as expected, offers the most advantages to farmers in the production phase without changing the final product. This is supported by a 2000 report³⁰ on distribution of economic benefits from *Bt* cotton and herbicide-tolerant soybeans based on production in 1997. In the case of *Bt* cotton, the authors calculated the distribution of economic benefit for U.S. consumers at 7%, consumers in rest of world at 6%, U.S. farmers at 42%, Monsanto at 34%, and Delta & Pine Land (seed producer) at 9%. In the case of herbicide-tolerant soybeans, the distribution of economic benefits for U.S. consumers was 4%, consumers/producers in the rest of the world at 9%, U.S. farmers at 76%, Monsanto at 7%, and seed companies at 3%. In the future, spliced-DNA crops will need to focus on increasing the benefits to consumers.

Trade

The adoption of the Cartagena Protocol on Biosafety has introduced a new dimension to the global governance of biotechnology and is now a major factor in the global flow of biotechnology products and processes. The moratorium on transgenic crops by the European Union and their labeling requirements has effectively blocked imports of spliced-DNA crops into many European countries. Undersecretary of State Alan P. Larson has estimated that the European Union restrictions are costing U.S. companies \$4 billion a year in global trade.³¹ A comprehensive review of the results of

²⁹ Carpenter, Janet E. and Leonard P. Gianessi. 2001. Agricultural Biotechnology: Updated Benefit Estimates. National Center for Food and Agricultural Policy. Washington, DC www.ncfap.org.

³⁰ Falck-Zepeda, Jose B., Gref Traxler, and Robert G. Nelson, 2000. Rent Creation and Distribution From Biotechnology Innovations: The case of *Bt* Cotton and Herbicide-Tolerant Soybeans in 1997. *Agribusiness* 16: 21-32. John Wiley & Sons, Inc.

³¹ Spiess, Alan and Marc Kaufman, Washington Post, August 26, 2001.

EC-supported research into the safety of genetically modified organisms found that there were no new risks to human health or environment beyond the usual uncertainties of conventional plant breeding.³² Brazil also prohibits the importation of spliced-DNA crops. Other countries are still apprehensive about the importation of spliced-DNA products and some like Japan require labeling. More recently, a trade dispute with China, a new member of World Trade Organization (WTO), over requiring safety certification of imported crops and food ingredients raises fears that it will halt the import of genetically modified crops.³³ It imports about \$1 billion worth of U.S. soybeans each year. It is also interesting to note that China began commercial production of new biotechnology crops in 1990 and is now the fourth largest producer of spliced-DNA crops in the world. These restrictions labeled as safety issues in reality may constitute a wall of import protectionism to get around the WTO requirements of lowering tariffs and opening its market to other WTO members. Currently, the trade impact to California cotton farmers has been minimal but it does pose a serious concern to the export of other California crops developed through new biotechnology.

ETHICS AND AGRICULTURAL BIOTECHNOLOGY

The emergence of biotechnology has featured debates on concerns over ethics, social, political, and equity issues that influence choice and policy particularly between industrial and developing countries. There are two kinds of ethical objections to the new biotechnology: extrinsic and intrinsic.³⁴ Extrinsic objections consider that the new biotechnology is too risky and that the potential harms outweigh the potential benefits. Intrinsic objections consider that the new biotechnology is unnatural (crossing species boundaries) even if the

benefits outweigh the harms. Consumers often take the following precautionary responses:

- When faced with two contrasting opinions about issues related to food safety, consumers place greater emphasis on negative information. They do so even if the source of the negative information is known to be unscientific or biased.
- This effect appears to be particularly strong when a consumer sees little to gain from a new food technology or when a given food is plentiful, it is rational to place extra weight on negative information about any particular piece of that food.

Comstock concludes that, although intrinsic arguments to ban new biotechnology products are not sound, the extrinsic concerns about potential consequences are sound and that we should continue to test and monitor non-substantially equivalent new biotechnology products to ensure the benefits outweigh the risks. These ethical principles were proposed:

- Ensure that all stakeholders are heard;
- Maintain a safe, nutritious and plentiful food supply;
- Preserve ecosystems; and
- Balance agricultural production and wise stewardship of the earth.

These principles were touched upon in a recent 2002 report from the National Academy of Sciences on transgenic plant regulations. This report called for an enhanced regulatory process for transgenic plants. It also called for greater public input and an enhanced scientific peer review along with the presentation of data and methods behind the regulatory decisions. These principles will also have an impact on the development of food biotechnology in California.³⁵

³² European Commission (2001). EC-Sponsored Research on Safety of Genetically Modified Organisms: A Review of Results. <http://europa.eu.int/comm/research/quality-of-hre/gmo/>.

³³ Iritani, Evelyn, Los Angeles Times, February 9, 2002.

³⁴ Comstock, Gary. 2001. Ethics and Agricultural Biotechnology: Intrinsic and Extrinsic Objections to GMOs. A Speech at the NABC 2001 National Conference Meeting May 22-24, 2001. Chicago, IL.

³⁵ Could, F. et al, Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation, February 2002, National Research Council, National Academy Press, Washington, D.C.

GLOBAL ACCEPTANCE AND DEPLOYMENT OF SPliced-DNA CROPS

The International Service for the Acquisition of Agri-biotech Applications (ISAAA) is an international network (CropBiotech.Net) that collects data on the global adoption of commercialized transgenic crops from a legion of colleagues from the public and private sectors in industrial and developing countries.³⁶ ISAAA data seems to be the most recent and reliable information on the production of GM crop plants and will be used here. China began commercial production of GM Crops (virus resistant tobacco and tomato) in the early 1990s. The first transgenic crop commercialized in the U.S. was the Flavr Savr tomato in 1993/1994. The first global production records begin in 1996 when about 4.3 million acres of GM crop plants were grown globally. During the last five years, 1996 to 2000, the production acreage of GM crop plants grown globally increased to about 109.2 million acres (Table 1). Of the 109.2 million acres, the U.S. grew about 73 million acres of transgenic crops. The USDA estimates for 2001 suggest that the U.S. acreage of soybeans will reach 63% of the total soybean acreage in the U.S. Biotech cotton reached 64% of the total acreage and corn 24% of the total

acreage. Globally transgenic crops were grown in 13 countries in all six continents during the year 2000: in descending order of area were the United States, Argentina, Canada, China, South Africa, Australia, Romania, Mexico, Bulgaria, Spain, Germany, France, and Uruguay. The geographical distribution of commercialized transgenic crop production and ongoing field testing in 2000 is shown in Figure 2. Although in the period through 2000 about 85% of the transgenic crops have been grown in the industrial countries, in the last year the production of transgenic crops in developing countries grew more rapidly than in industrial countries. These data suggest that the adoption of transgenic crops in the developing countries is moving more rapidly than many critics have suggested (Figure 3). This is to be expected because the adoption of any new agricultural technologies by developing countries usually lags behind the industrial countries because of the expense of research, testing, and regulation. They usually wait until the United States approves such technology before going ahead and approving it for their own country.

	Hectares (million)	Acres (million)
1996	1.7	4.3
1997	11.0	27.5
1998	27.8	69.5
1999	39.9	98.6
2000	44.2	109.2

Source: Clive James, 2000 (1).

Table 1: Global area of transgenic crop plants grown from 1996 to 2000

³⁶ James, Clive (2000). Global Status of Commercialized Transgenic Crops:2000. ISAAA Briefs No. 21. Preview. ISAAA, Ithaca, N.Y.

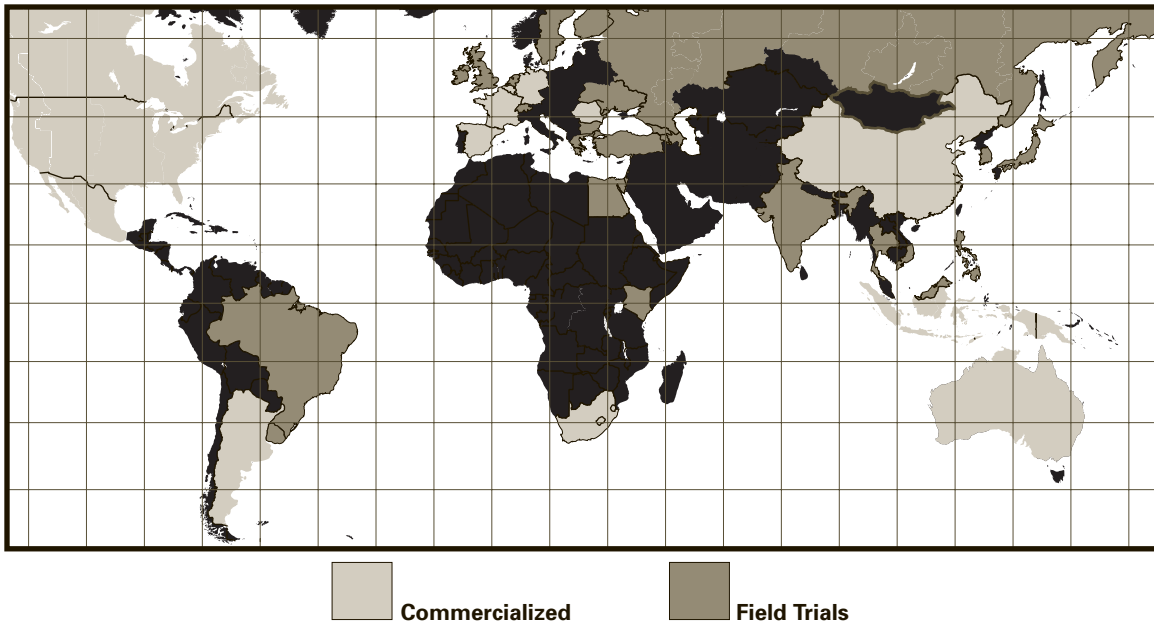


Figure 2. Global status of transgenic crop commercialization and field testing 2000

Source CropBiotech.net

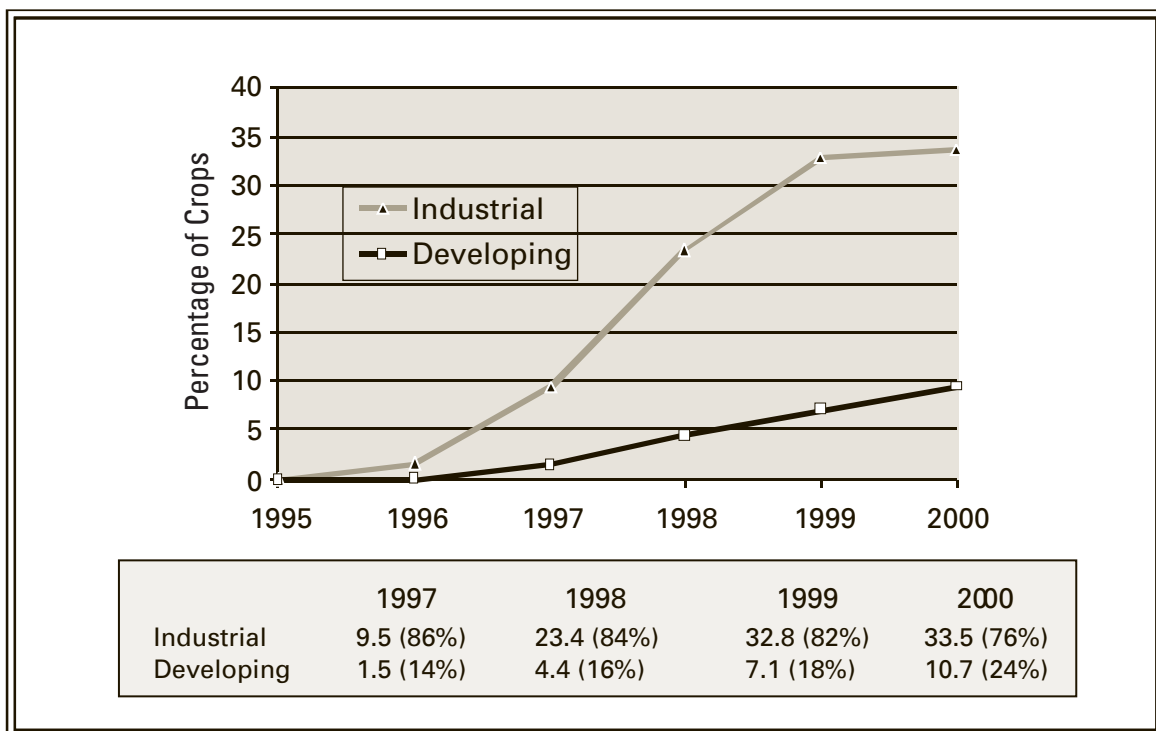
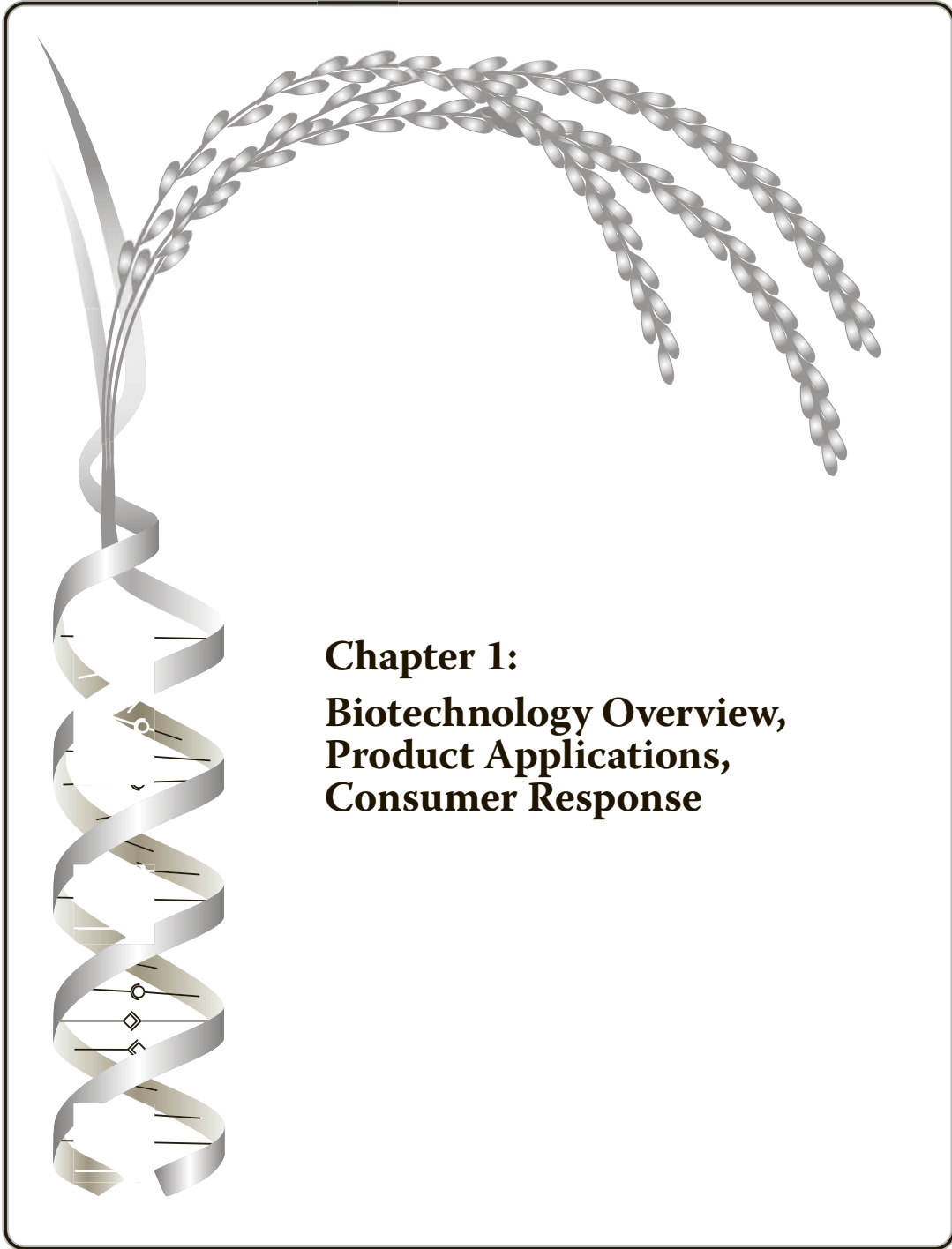


Figure 3. The global area of transgenic crops from 1996 to 2000 (mha) in the industrial and developing countries

Source: CropBiotech.Net www.isaaa.org



**Chapter 1:
Biotechnology Overview,
Product Applications,
Consumer Response**

Chapter 1: Biotechnology Overview, Product Applications, Consumer Response

Christine M. Bruhn, University of California, Davis

Biotechnology has an impact on our lives now and in the future. Today products modified by the newer techniques of biotechnology are in the supermarket, drug and retail stores. Additional products are being developed which offer advantages to farmers, the environment, and human health. Farmers often benefit from increased yields on the same acreage, decreased production costs, less exposure to insecticides and herbicides, and more flexibility in crop rotation. Consumers could benefit from foods with longer shelf life, less spoilage, the potential for lower prices at the supermarket, and improved nutritional characteristics. In the future, people with allergies may find the proteins that trigger allergic reactions have been removed, so they can enjoy previously prohibited foods. Those concerned with the environment will appreciate less insecticide and herbicide use, increased use of no-till agriculture, and the potential for less de-forestation because food demand can be met through increased yields on existing farmland.

While these benefits are appealing, any change encompasses both risks and benefits. This paper focuses on food applications of biotechnology, potential benefits, potential risks, strategies designed to minimize risks, and consumer response.

OVERVIEW: THE SCIENCE OF BIOTECHNOLOGY

Humans have selected and modified plants and animals since the beginning of civilization. The history of cultivated wheat illustrates how breeding and natural selection have produced the products we use today. The seeds of wild wheat dispersed when their brittle seed heads shattered. In the early stages of domestication, perhaps 10,000 years ago, natural variation (mutation) occurred in some wheat produced seeds that did not naturally shatter. Seeds from these plants were easier to gather than those which scattered on the ground. Without human intervention, this

mutated wheat would probably not reproduce successfully. Because of easy gathering, wheat with this characteristic was widely planted by early humans. Over the years, people selected varieties with improved characteristics, such as greater yield, length of growth cycle, and characteristics of the end product, such as durum wheat for making pasta, and hard and soft wheat for use in different baked products.

Field corn, sweet corn, Indian corn, and pop corn all were derived by natural variation from teosinte, the corn's ancestor. This plant, found in Mexico, contains a few hard seed kernels on a grass-like stock. Similarly, humans selected desirable characteristics in domestic animals and developed specific breeds seen today in dogs, cats, cattle, horses, chickens, and other animals.

Traditional and newer methods of crop improvement rely on genetic diversity in the starting population. Cross breeding may produce a new species that contains all the genes from the original parents. Triticale, a wheat-rye hybrid developed in the 1970s, is this type of hybrid. Alternatively, new plants may contain many of the genes from one of the parent plants and randomly chosen genes from the other parent. This is the method used to produce most hybrid plants grown today such as tomatoes and cotton.

Newer more precise methods of modification include a group of techniques that have evolved because of increased understanding of genetic information. Biotechnology, also called genetic engineering, genetic modification, or gene splicing, is the most recent development in this area.

Scientists have discovered that DNA or deoxyribonucleic acid contains the code that regulates the structure and function of organisms and the processes of life. Organisms receive this biological information from the order of four chemicals in their DNA. The length and sequence

of groups of these chemicals determines the genetic code. The central life functions of all organisms are nearly identical. The products of the genes that encode similar traits in different organisms are often similar in protein sequence. Most genes do not have characteristics specific to the organism, i.e. specific to fish or specific to tomatoes, and the organism from which a gene originated can not be determined by examining the gene sequence alone. In other words, there is no way to identify the difference between a fish gene, tomato gene, or human gene by looking at the gene alone. The uniqueness of an organism is due to the DNA sequences of their genes, the total organization of the genes, and the time and extent to which each gene is expressed.

When scientists identify the code responsible for a particular characteristic, that code can be transferred to other organisms. The segment of DNA which codes for the desired trait is snipped off and combined in the appropriate location with the DNA from another organism to form a new DNA molecule. This is called *recombinant* DNA (rDNA). Recombinant DNA is a widely used technique of biotechnology. Other techniques that do not include DNA splicing are also used.

To imagine how this process works in a more familiar context, consider DNA as the biological equivalent of a videotape. Like videotape, DNA carries information that can be transcribed, copied, and even cut out and spliced back in. A modified videotape with information rearranged from the original or a tape with a segment of another tape spliced in would be called the *recombinant* videotape. As videotape information is translated from electromagnetic signals into pictures and sounds, so DNA is translated from molecular signals (genes) into proteins that direct the cell's functions and determine its characteristics.

Comparison: Traditional Breeding and the New Biotechnology

Modern biotechnology using rDNA techniques is more versatile than traditional breeding. In the past, genetic changes were limited to changes within the same botanical family or animal family, such as wheat to wheat or sheep to sheep.

By using recombinant DNA, a gene from the same or different family may be transferred, as long as the change is compatible with the recipient organism.

Biotechnology is also more precise than traditional breeding. In traditional breeding, DNA from the parent plants or animals randomly combines so undesirable traits like lower yield, poor flavor, or even production of potentially toxic compounds, could combine with desirable traits. With biotechnology, those segments of DNA that code for a specific desirable characteristic can be selected and recombined in the new organism.

Traditional breeding programs are time consuming and labor intensive. Plants, for example, must be crossed again and again to breed out undesirable characteristics. While understanding the genetic code and learning techniques of transfer require significant time and scientific skill, once the code that determines a desirable trait is identified, that trait alone can be transferred. The precision and versatility of biotechnology enables changes in food quality and production to take place sooner.

Methods of Transfer

Plant modification using rDNA techniques uses one of two methods: free-DNA and T-DNA. In the free-DNA method, DNA carrying the gene of interest is shot into cultured plant cells. This method allows the introduction of precise DNA sequence; however, it is not possible to predict exactly where the sequence will be integrated. In the T-DNA method, a non-pathogenic DNA from bacterial, *Agrobacterium tumefaciens*, carries the desired genes into the host cell chromosome. This method greatly increases the precision of DNA insertion.³⁷

REGULATION, ENVIRONMENTAL AND HUMAN SAFETY

In 1992, the Food and Drug Administration (FDA) established a policy of testing and regulating human food and animal feed developed through the new techniques of biotechnology. Food and feed must meet the same safety standards

³⁷ Institute of Food Technologists. IFT Expert Report on Biotechnology and Foods Chicago, IL, 2000.

regardless of method of production. Nevertheless, those developing a food modified by the newer methods of biotechnology were advised to voluntarily consult with FDA prior to introducing the food in the marketplace. All developers have followed this policy. By the end of 2000, 50 new rDNA biotechnology foods were evaluated in FDA's voluntary consultation process. In May 2000, FDA announced that the consultation process would become mandatory.³⁸

Pharmaceuticals and human vaccines are also regulated through FDA. The United States Department of Agriculture (USDA) regulates vaccines for animal use. Product evaluation is based upon laboratory and clinical testing which demonstrate safety and effectiveness of the products for their intended use.

Field testing and commercial sale of agricultural biotechnology crops are regulated by the Animal and Plant Health Inspection Service (APHIS) within USDA. This group also regulates plant pests. APHIS will only grant a permit if it determines that the plant poses no significant risk to other plants in the environment and is as safe to use as more traditional varieties.

Regulating pesticides, setting environmental tolerances for pesticides and establishing safe levels for pesticide use is the responsibility of the Environmental Protection Agency (EPA). This agency measures the aggregate risk from dietary exposure and other non-occupational sources of exposure. EPA must focus on exposures and risks to infants and children and assume an additional safety factor to account for uncertainty in data and laboratory animal to human variations. If EPA determines there is reasonable certainty that no harm will result from exposure to a particular residue, then the residue level will be considered safe. In 1994, EPA proposed that the regulatory process focus on the pesticide and not the plant. Plants are subject to regulation only if they produce pesticidal proteins as a result of modification with rDNA techniques. In April 2000, the National

Research Council issued a report accepting EPA's regulatory approach. However, concern was expressed by 11 major scientific societies representing more than 80,000 biologists and food professionals. These societies warned that the EPA policy would discourage development of pest-resistant crops and prolong or increase the use of synthetic chemical pesticides. The EPA policy, they reported, would increase the regulatory burden for developing pest-resistant crops, limit the use of biotechnology to large developers who can pay the high regulatory costs, and handicap the U.S. in international markets.

FOOD APPLICATIONS, POTENTIAL BENEFITS

Applications Which Have Entered the Marketplace

The first rDNA biotechnology derived-plant product introduced into the United States was the Flavr Savr tomato, introduced in 1994. Using the T-DNA technique, a reverse (called "antisense") version of a code which produces an enzyme responsible for fruit softening was introduced into the tomato. By inserting the reverse code, less of the softening enzyme was produced. It was expected that the tomato could stay on the vine longer, develop a fuller flavor and still be firm enough for shipment to the market. The Flavr Savr was not a commercial success in the U.S. for a variety of reasons; however, a processing variety of tomato with the antisense gene was used in processed products because it had a higher solids content and required less energy to process into tomato paste. Tomato paste clearly labeled, "Made with Genetically Modified Tomatoes, and the benefits of using genetically modified tomatoes for this product are less waste and reduced energy for processing" was successfully marketed in the United Kingdom supermarkets for several years.

The first biotechnology modified ingredient introduced into the food chain was a substitute for a traditional enzyme used in cheese manufacturing. The enzyme, rennet, is added to milk in the production of many hard cheeses like cheddar, mozzarella, and jack. Traditionally rennet is extracted from the stomach of a non-weaned calf. This enzyme varies in efficiency and quality and may be very costly, depending on the supply of slaughtered calves and the demand for

³⁸ US Department of Health and Human, S. FDA to strengthen pre-market review of bioengineered foods: US Department of Health and Human Services, 2000. <http://www.fda.gov/bbs/topics/news/new00726.html>.

cheese. This enzyme can be exactly replicated by microorganism using techniques of biotechnology. The resulting enzyme, chymosin is consistent, high quality, and more economical than rennet. Chymosin is used in over 80% of the hard cheeses produced in the United States and Canada.

Another early application of biotechnology was the supplementation of dairy cows with a natural hormone, bovine somatotrophin (BST) produced through the techniques of biotechnology. Over the lactation cycle, cow production of milk decreases. If supplemented with rBST, (BST created by recombinant techniques) and provided additional feed, production will return to high levels for some cows. Numerous studies demonstrated that milk from cows supplemented with rBST was no different from milk from non-supplemented cows. Additionally cow health was not jeopardized by supplementation. The FDA decision on the safety of milk produced by supplemented cows was endorsed by numerous health authorities including the American Dietetic Association and former Surgeon General C. Everett Koop. Processors are permitted to label milk and dairy products produced from non-supplemented cows. To avoid consumer misconception, the label must also acknowledge that the FDA is not aware of any evidence indicating a difference in quality or wholesomeness between milk from supplemented and non-supplemented cows.

Other biotechnology modified plant products introduced in the United States include squash resistant to some strains of mosaic viruses, insect-resistant potatoes, corn and cotton, and herbicide-tolerant corn, soybeans and canola. Insect protection helps reduce the use of insecticides because the plants themselves produce proteins necessary to prevent insect damage rather than depending on the application of chemical sprays. For example, during the first three years of commercial availability of insect-protected cotton, experts estimate that approximately one million gallons of insecticide were *not* applied to U.S. cotton fields.³⁹ Better protection from insects also helps reduce crop disease and improve crop quality. For example, several recent studies demonstrate

that insect-protected corn contains lower levels of fumonisin, a naturally produced mycotoxin that diminishes the food and feed quality of corn products.⁴⁰

Ring spot virus was destroying papaya trees in Hawaii. Using techniques of biotechnology, virus resistance was transferred to several varieties of papayas in Hawaii where the virus was firmly established. The virus resistant trees thrived, reviving the papaya industry by permitting the production of high-quality fruit.

Applications Under Development

Stronger Plants, Increased Crop Yield

Plant breeders will continue to explore ways to protect crops from devastating disease. Some under investigation include resistance from fire-blight which constrains production of apple and pears. Research is also underway to enable plants to increase resistance to salt, drought, and exposure to heavy metals such as aluminum.

Plants can be modified to grow in marginal soil and can also be used to remediate soil. Toxic metals such as aluminum and manganese, present in acidic tropical soils, reduce root growth and crop yield by as much as 80%. Scientists have demonstrated that modifying a plant to produce citric acid enables them to increase yields.⁴¹ Plants have also been modified to grow in high salt environments, enabling the plant to grow in otherwise unusable land.⁴² Furthermore, the plant concentrates salt in the leaves, providing an agronomic way to reduce salt in the soil and increase suitability for other crops.

Improved Nutrition

Specific foods are being developed to help overcome nutritional problems unique to different regions of the world. The most widely known

³⁹ Institute of Food Technologists, 2000.

⁴⁰ Dowd, P.F., Bartelt, R.J., Behle, R.W., McGuire, M.R., Lagrimini, L.M., Estruch, J.J., Kendra, D.A., Hill, M., Privalle, L.S., Wright, M., Molid, G., Hasse, I., and Duvick, J.P., 1999, *Advances in insect-oriented IPM of mycotoxigenic fungi in corn in the Midwest FY 1998*, Presented at Aflatoxin Elimination Workshop, St Louis, MO, Oct 25-27.

⁴¹ Institute of Food Technologists, 2000.

⁴² Zhang, H.-X.; Blumwald, E. 2001. Transgenic salt-tolerant tomato plants accumulate salt in foliage but not in fruit. *Nature Biotechnology*. 19:765-768.

application in this area is “golden rice,” which has been modified to increase the beta-carotene content, a precursor of Vitamin A, and iron. This application is directed toward the developing world where, according to the World Health Organization, vitamin A deficiency affects one quarter of a billion children with child death rates as high as one out of four in some regions of the world and iron deficiency affects 3.7 billion people.⁴³ While no one application will eliminate a severe nutritional deficiency, this type of product could help lessen the problem.

Research is on-going to identify and enhance beneficial bacteria commonly used in yogurt and other fermented dairy products. Selected strains of *Lactobacillus* and *Bifidobacterium* have been found to stimulate the immune system, lower blood cholesterol, protect against certain cancers, and provide other health enhancing functions.⁴⁴ Recombinant DNA techniques will help identify and reproduce those strains with the most health enhancing capability.

Reduced Allergenicity

The techniques of rDNA offer the potential to decrease or eliminate allergenic proteins. The level of a major rice allergen has been reduced using biotechnology. Ongoing research is focused on reducing the allergens in wheat and other common foods.

Medical Benefits

Plants may be used to produce edible vaccines and to increase the production of medical products important to human or animal health. Researchers have developed a system to use tobacco plants to produce a therapeutic vaccine against non-Hodgkin's B-cell lymphoma in mice.⁴⁵ A similar approach was used to develop a vaccine against insulin-dependent diabetes mellitus. Work is ongoing in other related areas.

⁴³ Gura, T., 1999, *The new genes boost rice nutrients*, Science 285:994-995.

⁴⁴ Sanders, M. 1999. Probiotics. *Food Technology*. 53(11):66-77.

⁴⁵ Arntzen, C.J., 1997, *High-tech herbal medicine: Plant-based vaccines*, Nature Biotech, 15:221-222.

Healthier Farm Animals

The nutritional content of animal feed may be improved through techniques of biotechnology. Plant breeders have used rDNA technology to develop a corn that is nutritionally more dense and easier for animals to digest.⁴⁶ Scientists are also developing feed with lower levels of phytate: this has environmental ramifications because it will reduce phosphorous, nitrogen, and odor from animal waste. Conversely, scientists have been able to modify pig saliva to more thoroughly digest nutrients.⁴⁷

Environmental Benefits

Farmers who plant crops modified for herbicide or insect resistance report less use of pesticides.⁴⁸ Farmers planting herbicide resistant crops may use only one application of the herbicide once weeds have emerged rather than multiple pre-emergence applications which may not correspond to weed growth. Furthermore, farmers are able to use more environmentally benign pesticides that break down into carbon dioxide and water. Herbicide-tolerant crops provide growers with more flexibility in controlling weed pests that can compromise yield because of competition for nutrients, sunlight, and water. In addition, this trait encourages implementation of conservation tillage practices that help preserve topsoil and reduce soil erosion and reduce the use of fossil fuels. A 1997 USDA study found that herbicide-tolerant soybeans reduced farm inputs costs by 3% to 6% and increased yields by 13% to 18% in most regions of the United States.⁴⁹

⁴⁶ Mazur, B., Krebbers, E., and Tingey, S., 1999, *Gene discovery and product development for grain quality traits*, Science, 285:372-375.

⁴⁷ Golovan, S.P.; Meidinger, R.G.; Ajakaiye, A.; Cottrill, M.; Wiederkehr, M.Z.; Barney, D.J.; Plante, C.; Pollard, J.W.; Fan, M.Z.; Hayes, M.A., et al. 2001. Pigs expressing salivary phytase produce low-phosphorus manure. *Nature Biotechnology*. 19(8):741-745.

⁴⁸ Institute of Food Technologists, 2000.

⁴⁹ Institute of Food Technologists, 2000.

Aids in Food Processing

Beneficial bacteria and enzymes are widely used in food processing.⁵⁰ These include bacteria, yeast, and molds that convert milk, cereals, fruit, vegetables, and meats into a wide range of products including cheese, bread, beer, wine, pickles, and sausages.

AREAS OF CONCERN

Any change has both benefits and liabilities. Following are some of the areas of concern associated with the newer techniques of biotechnology and their effect on agricultural production.

Agribusiness Consolidation and Competition

Some segments of the seed market have become highly concentrated. Large agricultural companies compete internationally for the market share in corn, soybean, oilseed, and vegetable seed markets. The market situation should be continually evaluated to avoid potential abuse of market power through antitrust policy if appropriate. If firms can enter the marketplace, price competition will help control the development of a monopoly.

Allergenicity

Most food allergies are caused by proteins from eight sources: milk, eggs, fish, crustaceans, peanuts, tree nuts, soybeans, and wheat. FDA policy requires that, if the source of a gene is from a known allergen, the producer must demonstrate that the allergen has not been passed to the new food. If this can not be demonstrated, the food must be labeled as containing genetic material from the allergenic food. This policy was successfully applied when scientists used Brazil nuts to increase the nutritional value of soybeans. The allergenic protein from the nuts was incorporated into the soybean. Rather than face the difficulty of segregating the market, development of this product was halted.

Corn modified by a new *Bt* protein was approved for animal feed but not human consumption because the developer had not demonstrated that humans would not develop an allergic reaction to the protein. Because this Starlink™ corn could not

be separated in the food chain, it was withdrawn from the market.

At this time, no unique allergic reactions have occurred in any of the foods derived through rDNA technology. It is possible to develop an allergic reaction to a food whether developed by traditional or newer technologies.

Antibiotic Resistance Transfer

Traditionally researchers used antibiotic resistance to identify new plants that contained new genetic material. In plant transformation, a marker gene for resistance to the antibiotic kanamycin was widely used. Some were concerned that the resistance could be transferred to a microorganism, thereby reducing the efficiency of this antibiotic. A joint consultation of the Food and Agriculture Organization and the World Health Organization concluded that there is no evidence that the marker poses a risk to humans or domestic animals. Antibiotic resistance transfer from plants to microorganisms is rare, but can not be completely discounted. In new products under development today, non-antibiotic resistance markers have replaced kanamycin.⁵¹

Contamination of Organic Crops

At this time, the organic farming industry has chosen not to permit products modified by rDNA technology. If an organic crop is planted near a transgenic crop of the same species, it is likely that some seeds produced from the organic crop will carry transgenic traits which may be detected by today's highly sensitive scientific tests. Planting a border of conventional crop will reduce the rate of pollen spread.

Decreased Genetic Diversity

The widespread adoption of rDNA modified soybean and corn could leave these crops susceptible to new epidemic pests and diseases. It would be appropriate to diversify the germplasm and assure an adequate backup of alternative varieties in the event of an unforeseen disaster. Germplasm collections should be safeguarded and farmers should be encouraged to plant a broad spectrum of plant breeds.

⁵⁰ Institute of Food Technologists, 2000.

⁵¹ Institute of Food Technologists, 2000.

Environmental Balance

All human activity including building homes and practicing traditional agriculture disrupts nature. New technology and traditional practices should be evaluated in a comprehensive rather than isolated fashion. A laboratory experiment suggested that monarch butterfly larval may be harmed by widespread use of *Bt* corn. The experiment found larval died when forced to feed on milkweed leaves heavily dusted with corn pollen containing the toxin. However, this experiment did not reflect real conditions which the larva encounter. In the field, monarch butterflies prefer to lay eggs on milkweed plants that are in the open and rain is likely to rinse pollen off before the larva feed. Field studies in Maryland, Iowa, Nebraska, and Ontario found that a lethal dose of *Bt* pollen spread only a few feet from corn plants. The EPA's suggestion that farmers plant a refuge area around the perimeter of the corn field and the limited movement of corn pollen virtually eliminates risk of *Bt* pollen to monarch butterfly larvae.⁵² In a suit initiated by Greenpeace, the U.S. Supreme Court ruled that beneficial insects like butterflies are more likely to survive when *Bt* crops are planted since they replace more lethal pesticide treatments.

Herbicide Resistance

There is concern that genes from a herbicide tolerant plant would spread via pollen to wild weeds, thus reducing the effectiveness of the herbicide. This is unlikely for soybeans, corn, and many other crops in the United States because there are no related wild weed species grown in the U.S. This is a concern for crops such as rice or sorghum because of related weed plants. The EPA evaluates the potential for cross-pollination before granting a permit to grow biotechnology modified plants.

L-Tryptophan

The dietary supplement L-Tryptophan is manufactured by bacterial fermentation. During manufacture, it becomes contaminated by other substances that are removed by treatment with

activated carbon and reverse osmosis.⁵³ In 1988, a Japanese company made several changes in their manufacturing practices, including the use of genetically engineered organisms to produce the L-Tryptophan. At the same time the firm changed their purification procedures, eliminating the use of reverse osmosis and reducing the amount of activated carbon. The illness of 1,500 people and the death of 37 were traced to this company's product. Some have attributed these deaths to the use of genetic engineering, while others state the change in safety was a result of changes in the purification procedure.^{54, 55, 56} Genetic engineering organisms are widely used to produce the highest quality human medicines including human insulin. There is no evidence of increased risk from use of rDNA technology.

Naturally Occurring Toxicants

Most plants and many animals produce or carry naturally occurring toxic substances. Most of these occur at such low levels that they are of no human health significance. More than 20 have resulted in well-documented reports of human injury or death.⁵⁷ Solanine, a neurotoxin in potatoes, has been the cause of outbreaks associated with potatoes. Solanine content varies by potato variety and is increased when potatoes are exposed to light. A new potato variety produced through traditional breeding with high levels of solanine was withdrawn from the market. Cyanogenic glycosides, found in foods such as lima beans and bamboo shoots, is another example of natural toxins in common foods.

⁵³ Institute of Food Technologists, 2000.

⁵⁴ Hill, R.H. Fr., Caudell, S.P., Philen, R.M., Bailey, S.L., Flanders, W.D., Driskell, W.J., Kamb, M.L., Needham, L.L., Sampson, E.J., 1993, *Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome*, Arch. Environ. Contam. Toxicol., 25(1):142-143.

⁵⁵ Kilbourne, E.M., Philen, R.M., Kambmm M.L., Falk, H., 1996, *Tryptophan produced by Shava Danko and epidemic eosinophilia myalgia syndrome*, Rheumatol, 46 (Suppl): 81-91.

⁵⁶ Philen, R.M., Hill, R.H. Jr., Flanders, W.D., Caudell, S.P., Neeham, L.L., Sewell, L., Sampson, E.J., Faulk, H., Kilbourne, E.M., 1993, *Tryptophan contaminants associated with the eosinophilia myalgia syndrome*, Am. J. Epidemiol, 138(3):154-159.

⁵⁷ Institute of Food Technologists, 2000.

⁵² Institute of Food Technologists, 2000.

It is appropriate to evaluate new foods produced by conventional techniques or newer methods for the presence of natural toxins. While products developed by traditional techniques seldom undergo this evaluation, those produced via biotechnology are carefully scrutinized. For example, extensive data submitted on the Flavr Savr tomato demonstrated that the level of the natural toxin, tomatine, was comparable in the new variety with those currently in the market place.

Pest Resistance

It is common for insects to develop resistance to any pest control method over time. Scientists are testing a variety of strategies to extend the useful life of pesticide. To delay development of resistance to *Bt*, plants are produced with more than one form of *Bt* and farmers are advised to plant some conventional seeds to serve as an insect refuge.

Virus Resistance

Recombination between a viral transgene and another virus to create a new virus with enhanced virulence is a scientific possibility. A National Research Council committee concluded that "most virus-derived resistance genes are unlikely to present unusual or unmanageable problems that differ from those associated with traditional plants."⁵⁸ Therefore, this possibility is no more likely to occur using techniques of biotechnology than using traditional techniques.

CONSUMER RESPONSE

Consumer response to biotechnology in the United States is generally positive; however, many know little about this technology and some question its risks and benefits.^{59, 60, 61, 62} A 2001 national survey of 1,004 U.S. adults found that only 36% were aware that products modified by biotechnology were in the supermarkets.⁶³ When asked what products were in the market, most mentioned vegetables, especially tomatoes. Since rDNA modified soybeans, corn, and canola are widely planted and many food products

contain oil, corn, or soybean-based ingredients, as much as 70% of processed foods could contain ingredients that originated from rDNA crops. Therefore, it appears that consumers are not aware of the widespread use of products modified by these newer techniques.

Nevertheless, most U.S. consumers have a positive attitude toward biotechnology with 64% believing they and their families will benefit from biotech within the next five years.⁶⁴ Furthermore, 70% of consumers indicate they would purchase produce modified by biotechnology to reduce pesticide use, 66% would purchase produce modified to contain more vitamins and nutrients and 58% would purchase products modified for better taste.^{65, 66} Consumers also indicate support for other applications of biotechnology with 82% supporting use of this technology to enable trees to grow faster and 81% supporting applications in which plants would use less water.

While most consumers are positive, 15% to 20% indicate they are not at all likely to select products modified by biotechnology for any of these purposes.^{67, 68} Focus group discussion, half of which were composed of concerned consumers,

⁵⁸ Institute of Food Technologists, 2000.

⁵⁹ Abt Associates Inc. 1996. *Trends in the United States, consumer attitudes and the supermarket*. Washington DC. 91p.

⁶⁰ Hoban, T.; Kendall, P. 1993. *Consumer attitudes about food biotechnology*. Raleigh, North Carolina pp. 36.

⁶¹ Wirthlin, W. More US consumers expect biotech benefits: International Food Information Council, 2001. <http://ific.org>.

⁶² Levy, A.S., Derby, B.M., 2001, *Report on consumer focus groups on biotechnology*, <http://www.cfsan.fda.gov>.

⁶³ Wirthlin, 2001.

⁶⁴ Wirthlin, 2001.

⁶⁵ Grabowski, G. GMA survey shows Americans learning more about biotechnology: Food consumption patterns unchanged: Grocery Manufacturers of America, 2000, www.gmabrands.com/news/docs/NewsRelease.cfm?DocID-645&.

⁶⁶ Wirthlin, 2001.

⁶⁷ Council for Biotechnology, I. 2001. *Good Ideas are Growing*. Personal communication.

⁶⁸ Wirthlin, 2001.

indicated that people viewed biotechnology as offering both benefits and risks. Fear of unknown long-term consequences was the most frequently mentioned concern.⁶⁹

A national survey completed in 2002 found 85% to 88% of people rated environmental benefits of average or high importance, with ratings in California comparable with the national rating.⁷⁰ The greatest support was accorded, "Genetically modifying plants so that they can clean up toxic pollutants in the soil," with 74% rating this attribute as important and 14% of average importance. Other benefits rated were "Reducing the amount of fertilizer that can pollute streams and lakes," 72% and 15%; "Reducing the amount of water used to grow crops," 68% and 17%; "Developing disease-resistant varieties of trees that are threatened or endangered," 67% and 19%; "Reducing the need to log in native forests," 63% and 19%; and "Reducing the amount of chemical pesticides," 61% and 24%.

Consumer response to potential risks was also evaluated. Fewer people rated risks important than rated benefits important. "The possibility that the genes could contaminate ordinary plants, fish, and trees," was rated important by 64% and average importance by 18%. Other risks and their ratings were: "Creating superweeds," 57% and 17%; "Increasing the number of insects that may develop resistance to pesticides," 57% and 17%; "Reducing genetic diversity," 49% and 22%; "Changing plant/fish/tree through biotechnology so that it might harm other species," 49% and 42%; and "Changing the ecosystem," 46% and 23%. Note, consumers did not volunteer these concerns, rather they responded to potential benefits and risks posed by the interviewer.

An assessment of European and American consumers found perception of risk and benefit and attitude toward moral acceptability influenced acceptance.⁷¹ Opponents viewed modification as

risky, the reason for modification not useful, and not morally acceptable. When asked to respond to specific food or agricultural applications, only 2% of American and European consumers found morally unacceptable applications perceived as useful and low risk.

Attitudes Toward Labeling

Labeling of products modified by biotechnology is not an issue of high concern among consumers. When 1,000 consumers were asked to identify food safety concerns, only 2% volunteered genetically modified foods.⁷² Similarly, when asked to voluntarily describe information they would wish to have that is not currently available on a food label, only 2% noted genetic modification.⁷³ When specifically asked what of several pieces of additional labeling information people might prefer, 17% identified genetically engineering, 16% indicated no additional information, 15% didn't know and 31% requested pesticide residue information.⁷⁴

Consumers want to be informed when new products are different from traditional ones. While it is unlikely that U.S. consumers are familiar with the FDA labeling policy that is based on this premise, 70% support the policy once it is explained.⁷⁵ On the other hand, an increasing number believe modified products should be labeled even if there is no nutritional or safety difference, with 40% holding this view in 1997 and 58% in 2001.

Labeling that does not provide adequate information can be misunderstood. Special labeling or use of the term "genes" influences consumer attitudes. A 2001 study found that 50% of consumers considered unsafe or were uncertain about the safety of a bread product labeled "Contains genes from wheat."⁷⁶ Since

⁶⁹ Levy and Derby, 2001.

⁷⁰ Pew Initiative, 2002, *Environmental savior or saboteur? Debating the impacts of genetic engineering*, <http://www.pewtrusts.com>.

⁷¹ Gaskell, G.; Bauer, M.; Durant, J.; Allum, N. 1999. Worlds apart? The reception of genetically modified foods in Europe and the US. *Science*. 285:384-387.

⁷² Wirthlin, 2001.

⁷³ Wirthlin, 2001.

⁷⁴ Bruskin. National opinion polls on labeling of genetically modified foods: Center for Science and the Public Interest, 2001. http://www.cspinet.org/new/poll_gefoods.html.

⁷⁵ Wirthlin, 2001.

⁷⁶ Bruskin, 2001.

products made from wheat could contain wheat genes, this true statement would raise consumer anxiety even though the product is identical to what has been available for years. Similarly, 35% of consumers believed a product was superior to a non-labeled product if the label stated “Does not contain genetically engineered corn.”⁷⁷ One could argue that the genetically engineered corn contained less mycotoxin than the traditional corn and may actually be safer. Most consumers are probably not aware of the mycotoxin content of corn and may reject a modified product out of apparent concern for products that are “engineered.”

If labeling were required, 61% of consumers reached by telephone survey in 2001 believed the whole foods (such as whole tomatoes) should contain labels, 53% of consumers believed major ingredients in a food should bear the label, 42% would also label minor ingredients such as corn starch in a mixed dish, and 38% would apply labeling regulations to any material from a modified product.⁷⁸ Consumers in focus groups, in contrast, found labeling of individual ingredients confusing.⁷⁹ If labeling were mandated, costs would rise if only to cover product tracing and verification. Only 44% of U.S. consumers said they would pay more for labeling of genetically engineered food.⁸⁰

U.S. consumers expect labeling to provide useful information. Any labeling scheme should use lay language, include the reason for modification, and indicate approval by recognized regulatory bodies. Disclosing the purpose for genetic modification can increase consumer perception of safety.⁸¹

People expect claims as to the absence of genetically engineered ingredients to be truthful.⁸² Although consumer perception of detection limit

has not been investigated in a quantitative survey, in focus group discussions people indicated that a produce labeled as not containing GM ingredients should have no trace of rDNA material when analyzed.⁸³ This is likely to be very difficult to achieve in today’s production and marketing environment.⁸⁴ In March 2002, the FDA deputy commissioner Lester Crawford stated, “If it’s on the label, it has to be true, and it’s up to us to be sure that it is.”⁸⁵ Crawford noted that it could be months or years before labeling rules are made final.

Since label claims must not be misleading, it is appropriate to clarify if a claim relates to safety or method of production. When labeling milk from cows not supplemented with rBST, the FDA suggested the statement, “No significant difference has been shown between milk derived from rBST – treated and non-rBST – treated cows.”

The label is only one means of providing consumers with information. Over 75% of consumers believed information other than labeling was a more appropriate method to inform the public.⁸⁶ Other avenues include television, newspapers and magazines, radio, web pages, and people to people exchange. Effective communication should be built on an understanding of the nature of consumer concerns. Information on biotechnology modifications should include the reasons for modification, degree of regulatory oversight, methods and extent of safety verification, and impact of modification on consumer safety and the environment.

SUMMARY

The scientific evidence indicates that there is no increased adverse health or environmental effect caused by the use of rDNA technology in

⁷⁷ Bruskin, 2001.

⁷⁸ Bruskin, 2001.

⁷⁹ National, Institute of Nutrition. 1999. *Voluntary labeling of foods from biotechnology. Report on a qualitative study among Canadian consumers.* Ottawa, Ontario

⁸⁰ Bruskin, 2001.

⁸¹ Bruskin, 2001.

⁸² Levy and Derby, 2001.

⁸³ Levy and Derby, 2001.

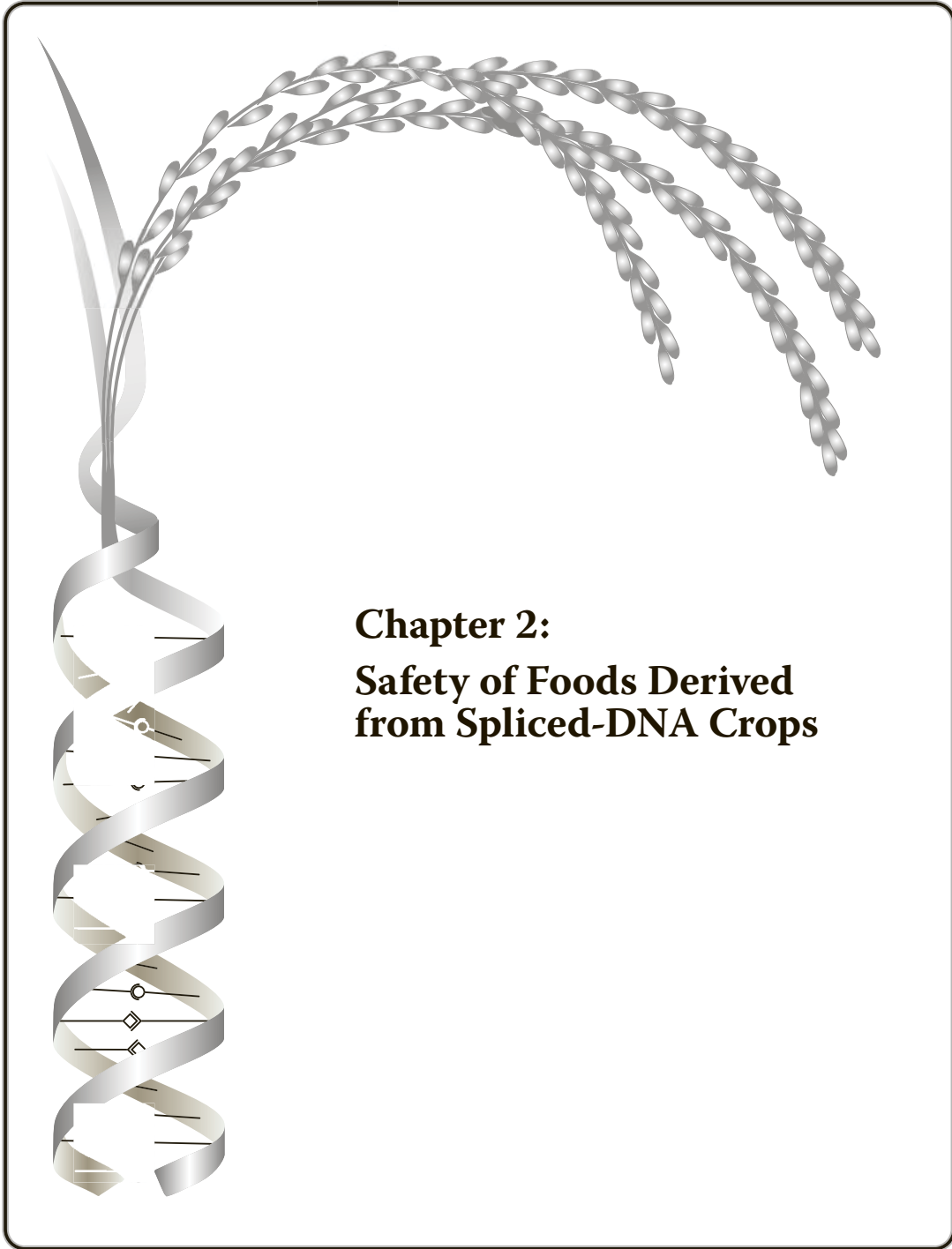
⁸⁴ Institute of Food Technologists, 2000.

⁸⁵ Brasher, P., 2002, Biotech food labeling delayed, Associated Press release, March 22.

⁸⁶ Wirthlin, 2001.

⁸⁷ Marvier, M., *Ecology of transgenic crops.* American Scientist, 2001. 89(2): p. 160-167.

agriculture and food production. This technique offers many benefits to human health, agricultural production, and environmental stewardship. Generally consumers are not aware of the current use of biotechnology in the agricultural arena; however, most value the benefits rDNA technology can help achieve and have confidence in scientific innovation. Some prefer to avoid products modified by biotechnology. The current guidelines for organic production prohibit use of rDNA technology, thus providing consumers the option to avoid these products.



**Chapter 2:
Safety of Foods Derived
from Spliced-DNA Crops**

Chapter 2: Safety of Foods Derived from Spliced-DNA Crops

George Bruening, University of California, Davis

It is convenient to consider two major categories, food safety and possible environmental effects, for the possible outcomes from commercialization of spliced-DNA crops and from the consumption of products derived from those crops. Food safety is the province of this chapter. Environmental effects are the subject of the next chapter.

Each spliced-DNA crop plant line (cultivar) approved by government regulators for commercial planting has one or more specific inserted genes. To date, the inserted genes have been of microbial origin. Each spliced-DNA cultivar is approved for planting in specific geographic areas with limitations on proximity to plantings of other spliced-DNA or conventional crops. Before approving registration, regulators examine the nucleotide sequence of the gene construction, expected new traits, history of experience with the corresponding untransformed cultivar, cultivation practices, and the expected processing methods and consumption of the crop product. That is, most regulation of spliced-DNA crops is in-depth and on a case-by-case basis. However, most objections to deploying spliced-DNA crops and to marketing spliced-DNA foods are general, raising issues about the safety of spliced-DNA technology and its products in all contexts. Conventionally bred crops are not subject to similar scrutiny or regulation, either specific or general. We consider issues of general risks that have been conjectured to be associated with spliced-DNA crops and food, information about specific spliced-DNA genes and food labeling for spliced-DNA content.

POSTULATED GENERAL RISK ASSOCIATED WITH TRANSGENIC CROPS

Extensive debate has surrounded the question of whether spliced-DNA crops products are qualitatively different from crops resulting from the non-spliced-DNA technologies described in the Introduction. Is spliced-DNA technology merely an extension of the numerous genetic modifications of crop species that have occurred

over the millennia through selection, mutagenesis, genetic crosses, marker-assisted breeding, and so on? On the issue of the novelty of transgenic crops, this chapter accepts the premise that crop transgene technology *is* qualitatively different from non-transgene technologies. This is the premise adopted by those who urge caution in, or oppose, commercial production from spliced-DNA crops. Spliced-DNA crops may be considered to be novel and to be distinct from conventional crops on several counts: the methods applied, the sources of genes, and the quantum improvements in conferred traits.

Assuming that spliced-DNA technology is qualitatively different from other crop genetic technologies, does this mean that the inherent risk associated with exploiting the newly introduced genes, or the degree of predictability in outcome, is different? Does the method by which a new DNA sequence is introduced into a crop plant have any material effect on the wholesomeness of the food derived from that plant? Or is it only the specific new DNA and traits conferred by that introduced DNA that are important? That is, do transgenic crops *in general* warrant closer scrutiny than crops genetically modified only by non-transgene methods?

TWO IMPLICIT HYPOTHESES

Those who are concerned with possible untoward effects of spliced-DNA crops generally, regardless of what new DNA sequences have been incorporated, appear to accept, whether stated or not, the validity of two hypotheses:

- (i) A gene, gene fragment or other DNA sequence from a taxonomically distant source, introduced into an uncontrolled location in the plant genome, results in a greater risk than a DNA sequence from a closely related source introduced by a genetic cross or DNA sequences modified by other conventional techniques; and

- (ii) adverse effects may appear only years or decades after widespread deployment of spliced-DNA sequences in crop plants, because current testing of spliced-DNA crops will likely fail to detect problems not currently recognized or problems that may appear later due to postulated variability, instability or delayed effects associated with spliced-DNA crops.

STATEMENTS FROM CRITICS OF SPLICED-DNA CROPS AND CROP PRODUCTS

Objections to spliced-DNA crop technology, based on the above hypotheses, have appeared frequently. Some critics urge mandatory labeling for spliced-DNA crop products or a moratorium or permanent ban on their planting. Some statements on these lines have appeared in well recognized journals or other respected venues.

Marvier⁸⁷ asks

“Do transgenic crops pose different risks from those common to crops created through traditional methods of plant breeding?”

and continues

“[G]enetic engineering can create many more combinations of genes and new traits than can traditional breeding. This greatly enhanced novelty diminishes anyone’s ability to predict the safety of a transgenic organism on the basis of past experience.”

The widely respected organization Consumers Union (CU) submitted a statement, promoting labeling of foods with a spliced-DNA origin, to the U.S. Food and Drug Administration (FDA).⁸⁸ The four main postulates and recommendations of the statement, paraphrased or quoted and condensed, are:

⁸⁸ Consumers Union, *Consumers Union’s comments on Docket No. 99-4248, Biotechnology in the Year 2000 and Beyond Public Meetings*. <http://www.consumersunion.org/food/fdacpi100.htm>. 1999, Consumers Union.

CU point 1. The location (positional effect) and degree of expression of a transgene in the spliced-DNA crop genome is uncontrolled. The plant transgene may be derived from a taxonomically distant organism with which the plant never will genetically cross. The synthesis in a plant of a protein from a bacterium or other non-plant source may result in a protein modified in a way unlike what was found in the source organism. These considerations anticipate unpredictability and instability and therefore require detailed and multigenerational analyses of the transgenic plant and long-term testing for toxicity of the transgenic plant product, including multiple year animal feeding tests.

CU point 2. The antibiotic gene introduced into the plant with the desired transgene may be transferred to other bacteria in the soil or in the human alimentary canal, thereby creating new, antibiotic resistant bacteria.

CU point 3. “Proteins are what cause allergic reactions, and virtually every gene transfer in crops results in some protein production. Genetic engineering will bring proteins into food crops ... whose potential allergenicity is largely ... unknown.”

CU point 4. “In the event that some unexpected difficulty should develop with an engineered food, labeling would facilitate identification of the problem. Labeling is also essential to the health and well being of individuals with food allergies and sensitivities.”

In summary, the Consumers Union statement contends that there is utility in a requirement for general labeling of food products for spliced-DNA origin, that is, labeling for a process *per se* rather than on the generally accepted basis of composition. Labeling for composition is reflected by specifications of total calories, calories from fat, and sodium ion content.

IS TAXONOMIC DISTANCE A USEFUL GUIDE TO RISK?

The first implicit hypothesis stated above must be placed in the context of the introduced DNA and the protein(s) encoded by the introduced DNA. As is described in the Introduction,

changes in the DNA sequences of a cultivated plant line (a “cultivar”), both localized and extensive, and new juxtapositions of DNA, are the lifeblood of crop genetic improvement. It is not difficult to erect and argue for a hypothesis that is the converse of hypothesis (i), that is, to postulate that a gene introduced from a closely related source presents a greater risk, not a lesser risk, than a gene from a distant source. Many genes encode proteins with multiple functions. The more closely similar are the organisms between which a gene is transferred, the more likely it is that at least one additional function of the introduced protein, among its potential multiple functions, will be effective in the organism to which the gene is transferred. Not all of the functions of a gene product may be known, and not all may be beneficial. Thus, a gene transferred from a taxonomically closely related source, for example by a wide genetic cross, could confer an unexpected and disadvantageous trait. In fact, there is no experimental evidence whatever in support either of hypothesis (i) or of the contrary hypothesis. A hypothesis alone is not sufficient to provide support for an objection in the absence of appropriate experimental evidence.

The unity of biology also argues against hypothesis (i). Although there are differences in the details, the residents of the biosphere of this planet are described by a single molecular biology. At the level of genes and metabolism, an elephant, a cotton plant and a bacterium are much more similar than they appear. There are no alien species on the planet. There is no reason to postulate, and no evidence for, a new biology associated with the introduction of taxonomically distant DNA into a plant because DNA is DNA and a gene is a gene. That is, the DNA of all organisms is comprised of the same nucleotide residues and, with only minor variation, nucleotide sequences specify proteins using the same genetic code. Taxonomic distance of the source of a gene and the recipient of a gene, alone, is highly unlikely to be of consequence in estimating the risk of introducing a new gene. DNA encoding a “benign gene” or DNA encoding a “toxic gene” could be obtained from the same species or genus as the recipient plant or from a species of a different kingdom or by chemical synthesis.

COMPARISON OF OUTCOMES FROM CONVENTIONAL AND SPLICED-DNA GENE TRANSFER

A comparison of the results from introducing the same gene by conventional breeding practice and by spliced-DNA method is instructive in the context of general objections to spliced-DNA crops. The value and the approach of wide genetic crosses are presented in the Introduction. We return to the example of cultivated tomato (*Lycopersicon esculentum*) improved by wide cross⁸⁹ to the wild tomato *L. peruvianum*. Extensive backcrossing to *L. esculentum* followed the wide cross to create cultivars. The home gardener may be familiar with the designation “VFNT” on a package of tomato seeds or a seedling pot stake. The “N” refers to resistance against the root-knot nematode (microscopic, root-invading worm) and “T” to resistance against *Tobacco mosaic virus* (TMV). Both traits were derived from *L. peruvianum*. “V” and “F” designated genes conferring resistance against fungi, *Verticillium* and *Fusarium*.

Regardless of how the wide cross is achieved, there is no control over which individual progeny accumulate which genes from each of the two parents. The plant breeder makes selections for the desired traits during the backcross series to the recurrent parent *L. esculentum*, thereby retaining the desired genes and gradually discarding other genes derived from the wild parent *L. peruvianum*. The VFNT tomato retains from *L. peruvianum* not only the selected gene or genes for resistance. Even after many backcrosses, considerable additional DNA from *L. peruvianum* is present in the derived *L. esculentum* line because of chromosome positional effects and “linkage drag.” Linkage drag results because the nucleotide sequences of DNA from *L. peruvianum* and the DNA from *L. esculentum* are sufficiently dissimilar in the regions of the desired genes that genetic recombination is suppressed.

For a typical VFNT *L. esculentum* cultivar, the *L. peruvianum*-derived N segment has more

⁸⁹ Smith, P.G., *Embryo culture of a tomato species hybrid*. Proceedings of the American Society for Horticultural Science, 1944. 44: p. 413-416.

than 3.5 million nucleotide pairs, compared to 945 million nucleotide pairs in the entire tomato genome. The N segment is small compared to the entire tomato genome, only three parts in 945 parts, about 0.3%. However, the N segment in the VFNT tomato is about 500 times larger than a gene, *Mi-1.2*, that the N segment contains and that alone is sufficient to confer resistance against the root-knot nematode in tomato.⁹⁰ That is, the method of wide cross and subsequent backcrosses transferred the *Mi-1.2* gene from *L. peruvianum* to *L. esculentum*, but linkage drag caused about 500 times more DNA, which likely includes a few tens of unknown genes, to be brought with *Mi-1.2*. Each of the other genes introduced from wild tomato by wide crosses similarly would be accompanied by many times the DNA necessary to confer the desired traits. The unknown genes encoded in the accompanying DNA could include genes specifying toxic proteins, allergenic proteins, or proteins that catalyze the synthesis of carcinogens or other undesirable compounds. Transfer of disadvantageous genes from *L. peruvianum* to *L. esculentum* is not a remote possibility, because the fruit and other parts of *L. peruvianum* plants are poisonous to humans.

A THOUGHT EXPERIMENT ON THE MERITS OF CONVENTIONAL BREEDING VERSUS DNA SPLICING

Imagine that the history of plant technology development was different than it is and that plant spliced-DNA technology and wide genetic crosses had been developed nearly simultaneously. The researcher desiring to transfer *Mi-1.2* from *L. peruvianum* to *L. esculentum* then would have had a choice of technologies, DNA splicing to transfer only the *Mi-1.2* gene or a wide cross and subsequent backcrosses to transfer the N segment of DNA. If commercialization of the resulting tomato line was to be subject to governmental regulation, regulators might specify which technology would be more acceptable. From the standpoint of food safety, there can be little doubt that the choice would be

DNA splicing. DNA splicing would introduce a 7000 nucleotide base pair segment encoding *Mi-1.2* rather than the entire 3.5 million nucleotide pair N segment encoding undocumented genes. Under current government regulations, a tomato line bearing *Mi-1.2* introduced by DNA splicing would be subject to scrutiny and regulation. A tomato line bearing *Mi-1.2* as part of the N segment of DNA would *not* require submission of data to any federal agency, much less scrutiny or regulation.

The potential reductions in risk attributable to the DNA-splicing approach do not arise solely from the small size of the introduced DNA segment. Assays for allergenicity or toxicity of a protein expressed in a plant usually rely on tests performed with the purified protein. For example, if a protein is digested to peptide fragments in less than 15 seconds when incubated in a solution designed to mimic the composition of gastric fluid, the protein is presumed not to be a food allergen.⁹¹ Generally, substantial fragments of a protein must pass through the stomach to the small intestine in order for the protein to be considered as a possible food allergen. In fact, even among proteins that digest slowly, most are found not to be allergenic. Purified protein is used for toxicity tests because the protein concentration in plant tissues generally is much too low to give any effect in toxicity tests using reasonable numbers of test animals. Purified test protein is added to plant-derived material to achieve a testable concentration. For the unknown genes introduced in a wide cross and not removed by backcrossing, the corresponding proteins are also unknown and therefore are not even available for the usual tests for allergenicity or toxicity. Thus, CU point 3 actually applies more closely to food from conventionally bred crops than to the target of the CU statement, food from spliced-DNA crops.

PHENOTYPE TESTING

The above comparison of the same gene introduced by two distinct methods exposes the fallacy of uniformly and generally regarding

⁹⁰ Milligan, S.B., et al., *The root knot nematode resistance gene Mi from tomato is a member of the leucine zipper, nucleotide binding, leucine-rich repeat family of plant genes.* Plant Cell, 1998. 10: p. 1307-1319.

⁹¹ Metcalfe, D. D., Astwood, J. D., Townsend, R., Sampson, H. A., Taylor, S. L. & Fuchs, R. L. (1996). Assessment of the allergenic potential of foods derived from genetically engineered crop plants. *Critical Reviews in Food Science and Nutrition* 36, S165-S186.

spliced-DNA crops as having greater risks than conventionally derived crops. This example also leads to a general consideration of the safety of food derived from crop plants that have been subject to genetic improvement of any type. As the Introduction to this report points out, virtually all of the food we consume is derived from genetically improved sources, whether plant or animal. On rare occasions, the progeny of conventional line crosses or wide crosses have presented a food safety or health problem. The classical case is celery. Both genetics and environment contributes to some celery producing an excess of furanocoumarins, which contribute to a photodermatitis of farm and grocery workers handling the vegetable and occasionally to a dermal photosensitivity of consumers of celery.⁹²

Why have researchers not observed any significant number of untoward effects from food recovered from cultivars that are derived from wide genetic crosses, induced mutations, and other alterations of DNA sequences? The answer probably lies in the practice of plant breeding and the need to achieve definition and uniformity of a cultivar before it is released. New cultivars are subject to “phenotype testing” by their developers. The phenotype is the aggregate of the characteristics of an organism, the convergence of the influence of genes and of the environment. Phenotype testing, which is not required for conventionally bred crops by any regulatory agency in the U.S., establishes whether a new cultivar is uniform in its behavior and is sufficiently improved over existing elite lines generally. Phenotype testing includes consideration of a range of characteristics that would reveal any substantial deviation of phenotype. In the long history of genetic crop improvement, the technology has been overwhelmingly benign, with only a few instances in which unfavorable characteristics of the food product came close to reaching, but did not reach, the market. In the brief history of spliced-DNA crops, no untoward effect on food safety has been documented.

⁹² Lombaert, G. A., Siemens, K. H., Pellaers, P., Mankotia, M. & Ng, W. (2001). Furanocoumarins in celery and parsnips: Method and multiyear Canadian survey. *Journal of AOAC International* 84, 1135-1143.

IS THE LOCATION OF A GENE IN THE CULTIVAR GENOME OF SIGNIFICANCE FOR FOOD SAFETY?

Current spliced-DNA technology provides no control over the location at which the spliced-DNA is inserted within the genome of the spliced-DNA plant. The position of insertion can be determined, where there may be an interest in doing so, by molecular genetic techniques. Under CU point 1 the position of the inserted transgene is postulated to have a significant influence on how the new transgene or pre-existing plant genes function, because of interruptions of pre-existing genes or new juxtapositions of DNA sequences. The genome is pictured as being composed of immutable DNA sequences encoding genes packed together. New juxtapositions of DNA sequences are created in conventionally bred plants as well as in spliced-DNA plants. DNA insertion, by various naturally occurring transposons, likely plays an important role in plant adaptation.^{93, 94} Half of DNA of the corn genome is composed of transposons and the remnants of transposons. The transposon-derived regions of the genome do not encode genes. Even the rice genome, which is among the smallest of all crop plant genomes, is derived almost 25% from transposons. Thus, crop plant genomes have very extensive regions in which gene insertion can be expected to have no untoward effect, because such regions already have undergone extensive insertion.

No adverse effects have been traced to position effects or new DNA juxtapositions in the genome of any spliced-DNA or conventionally bred cultivar. As is indicated in the Introduction, typically tens or hundreds of plants corresponding to distinct transformation events typically are derived from a single spliced-DNA experiment. Each such plant can give rise to a line of descendants, and the inheritance of the newly introduced, spliced-DNA gene can be assessed. Lines showing Mendelian inheritance are readily derived. No difference is observed in the inheritance of a spliced-DNA gene or an endogenous plant gene, suggesting no difference in genetic terms

⁹³ Kumar, A. and J.L. Bennetzen, *Plant retrotransposons*. Annual Review of Genetics, 1999. 33: p. 479-532.

⁹⁴ Wendel, J.F. and S.R. Wessler, *Retrotransposon-mediated genome evolution on a local ecological scale*. Proceedings of the National Academy of Sciences of the United States of America, 2000. 97(12): p. 6250-6252.

and providing no support for the unpredictability and instability anticipated by CU point 1. DNA insertion, of itself, is not a deleterious process, and it is not surprising that the unpredictability and instability anticipated by CU point 1 have not deterred the selection of elite spliced-DNA cultivars.

CU point 1 also suggests that a protein from a taxonomically distant source may be subject to protein modification in the crop plant that will confer unexpected, perhaps disadvantageous, properties on the protein. Protein modification is just one of the several ways in which the detailed molecular biology of prokaryotes (bacteria) and eukaryotes (plants, animals, yeasts, and other single-cell and multi-cell organisms whose cells have a nucleus) differ. One can raise other hypothetical risks to using spliced-DNA technology to introduce genes of bacterial or other microbial origin into crop plants. However, adverse or other unexpected and unintended effects that might be attributed to microbe-plant incompatibility have been observed only rarely in the many thousands of plant transgenic experiments that have been carried out in corporate and university laboratories over the past 15 years.⁹⁵ Unintended traits also appear from time to time in the progeny of conventional genetic crosses. The achieved and potential benefits of spliced-DNA crop technology appear to outweigh the risks from prokaryotic-eukaryotic differences, which until now have proved to be entirely conjectural and unlikely to escape detection in phenotype testing.

POSTULATED RISK FROM VARIABILITY AND INSTABILITY {HYPOTHESIS (II)}

CU point 1 and similar statements based on hypothesis (ii) speak of a supposed “variability” and “instability” of spliced-DNA constructions. The postulated instability sometimes is attributed to positional effects, as indicated in the previous two paragraphs, and sometimes to the *Cauliflower mosaic virus* 35S promoter that has been incorporated into most commercialized transgene constructions to provide high level production of the protein encoded by the transgene. These statements postulate that the

⁹⁵ Kuiper, H. A., Kleter, G. A., Noteborn, H. P. J. M. & Kok, E. J. (2001). Assessment of the food safety issues related to genetically modified foods. *Plant Journal* 27, 503-528.

plant, generations after transformation, will be unable to accommodate the foreign DNA.^{96, 97} Under this argument, rearrangements of DNA resulting from the supposed instability will result in the accumulation of mutations and DNA arrangements that will cause food safety or environmental problems. The process by which researchers generate a new Mendelian gene from spliced-DNA introduced into the transformed plant is described in the Introduction. It is certainly the expectation of researchers of companies that have invested in spliced-DNA technology that genes derived by spliced-DNA approaches will not differ significantly in their stability from conventional genes because stability is required to recover research investments.

There is no observation supporting the instability arguments. It is a fact that genes from taxonomically distant sources, e.g., the *Bt* gene from a bacterium as expressed in cotton or corn to provide insect control, do not function well when the unmodified, protein-encoding bacterial DNA sequences are transferred into the plant. However, this incompatibility is not a direct effect from the foreign DNA or its site of insertion in the plant genome. Rather, poor function is due to an incompatibility in the details of gene expression in bacteria and plants that often results in very low accumulation of a bacterial protein in the plant cell. Sufficient expression of the gene, e.g., sufficient accumulation of the *Bt* protein, was achieved by altering the nucleotide sequence of the DNA to make it compatible with plant gene expression.⁹⁸ That is, the bacterial gene is in effect converted to a plant gene that can direct the synthesis of the bacterial protein, in effect reducing the taxonomic difference in gene expression between the introduced transgene and other plant genes.

Statements on the supposed instability and variability of transgene and transgene function

⁹⁶ Ho, M.-W., A. Ryan, and J. Cummins, *Cauliflower mosaic viral promoter: A recipe for disaster?* Microbial Ecology in Health and Disease, 1999. 11: p. 194-197.

⁹⁷ Cummins, J., M.-W. Ho, and A. Ryan, *Hazardous CaMV promoter?* Nature Biotechnology, 2000. 18: p. 363.

⁹⁸ Perlak, F. J., Oppenhuizen, M., Gustafson, K., Voth, R., Sivasupramaniam, S., Heering, D., Carey, B., Ihrig, R. A. & Roberts, J. K. (2001). Development and commercial use of Bollgard(R) cotton in the USA: Early promises versus today's reality. *Plant Journal* 27, 489-501.

in spliced-DNA plants usually are made without context and sometimes with reference to the need to select transgenic lines with favorable traits from among many lines with less favorable or unfavorable traits. Both spliced-DNA and conventionally bred plant technologies produce individual plants with undesirable phenotypes. For example, a cross between tomato lines that was intended to transfer a gene for resistance against a fungus produced, from two normal parents, come lines that spontaneously developed necrosis as the plants matured.⁹⁹

POSTULATED RISK FROM DELAYED EFFECTS {HYPOTHESIS (II)}

Hypothesis (ii) is at the core of CU point 1 and commonly is buttressed by comparisons to experience with pesticides, as quoted above.¹⁰⁰ The comparison fails because of insufficient consideration for the chemical differences between organic pesticides and DNA or proteins. Organic pesticides are small molecules selected for their toxicity and sometimes for their stability. DNA molecules are not of themselves toxic, although a DNA molecule may encode a toxic protein. DNA and protein molecules are large and therefore inherently more delicate than organic pesticides. Proteins constitute a significant fraction of the mass of any cell, are the source of essential amino acids in our diet, and are the principal mediators of cell function. Among the many thousands of proteins with identified functions, the great majority are without toxic effect¹⁰¹ but a few are protein toxins, e.g., from vertebrate and invertebrate venoms and from some poisonous plants and microorganisms. Protein toxins characteristically are highly specific to their target and acute in their action,¹⁰² rather than chronic or cumulative. Organic pesticides generally are less specific than proteins with regard to target selectivity, meaning that non-target species are

far more likely to be affected by organic pesticides than by a protein toxin.

Proteins and DNA, in contrast to organic pesticides, are unstable and are readily broken down, in part, because they are food components. As food for humans or numerous other organisms in a food chain, protein is digested to peptides and to the fundamental units of peptides and proteins, the amino acids. Amino acids are synthesized into new proteins or are further metabolized to carbon dioxide and nitrogenous compounds. DNA is metabolized to nucleotides, which are degraded further. The digestion products of DNA and protein lack the functions of the intact molecules. There is no evidence that an intact protein can be consumed by an organism low in a food chain and be passed intact up the food chain. In contrast, organisms at the top of a food chain are able to accumulate certain organic pesticides in part because the pesticide chemical stability. There is no biological precedent for an analogy between 21st century spliced-DNA genes and gene products and 1940s organic pesticides with regard to delayed untoward effects.

The multiple year animal feeding tests demanded by CU point 1, rooted in hypothesis (ii) and the notion of similarity to organic pesticides,¹⁰³ would be unlikely to produce useful results because of the non-cumulative character of proteins. The extensive animal feeding studies that have been performed show no difference in digestibility or food value for transgenic plants compared to their untransformed counterpart and, in high dose feeding experiments, negligible toxicity for the product of the most commonly deployed transgene, *Bt* protein.^{104, 105}

⁹⁹ Langford, A. N. (1947). Autogenous necrosis in tomatoes immune from *Cladosporium fulvum* Cooke. *Canadian Journal of Research* 20, 35-64.

¹⁰⁰ Marvier, M., *Ecology of transgenic crops*. American Scientist, 2001. 89(2): p. 160-167.

¹⁰¹ Betz, F. S., Hammond, B. G. & Fuchs, R. L. (2000). Safety and advantages of *Bacillus thuringiensis*-protected plants to control insect pests. *Regulatory Toxicology and Pharmacology* 32, 156-173.

¹⁰² Sjoblad, R. D., McClintock, J. T. & Engler, R. (1992). Toxicological considerations for protein components of biological pesticide products. *Regulatory Toxicology and Pharmacology* 15, 3-9.

¹⁰³ Marvier, M., *Ecology of transgenic crops*. American Scientist, 2001. 89(2): p. 160-167.

¹⁰⁴ Betz, Hammond, and Fuchs, 2000. 32(2): p. 156-173.

¹⁰⁵ Sidhu, R.S., et al., *Glyphosate-tolerant corn: The composition and feeding value of grain from glyphosate-tolerant corn is equivalent to that of conventional corn (Zea mays L.)*. *Journal of Agricultural and Food Chemistry*, 2000. 48: p. 2305 -2312.

CLAIMS OF INSUFFICIENT REGULATION AND TESTING {HYPOTHESIS (II)}, COMPARISON OF CONVENTIONAL AND SPLICED-DNA CROPS

Testing has been a matter of interest from the earliest science-based evaluations of the safety of foods and food ingredients derived from plants and from microorganisms resulting from the application of spliced-DNA technology. The 1990 landmark work prepared by a multidisciplinary team assembled by the International Food Biotechnology Council¹⁰⁶ recommended that no additional regulatory measures were needed for products of traditional plant breeding practices and microbial mutagenesis and selection, and that foods and food products derived from non-traditional genetic modification techniques should be regulated as would their traditional counterparts. The report proposed criteria to ensure that food safety can be maintained and enhanced regardless of the methods used in their production.

The analyses presented in this chapter note the many similarities, and the little dissimilarity, between spliced-DNA crops and foods to their conventional counterparts. The concept of **substantial equivalence** has become widely accepted as a starting point for risk and safety assessments for spliced-DNA foods. A food product may be found to be substantially equivalent to a well characterized, reference food. Regulators may rule that a food judged not to be substantially equivalent will require analysis of toxicological and nutritional data and of allergenic potential in order to be considered for approval. The source of a new gene in the food will influence decisions about substantial equivalence. For example, a plant may be known to cause allergenic reactions, and all of its allergenic components may not have been identified. A gene or genes from such a plant might encode an allergenic protein, and relevant testing might be required.

¹⁰⁶ International Food Biotechnology Council. *Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification*. 1990. Regulatory Toxicology and Pharmacology, Vol 12, No. 3, 196 pp. Academic Press, Inc.

The concept of substantial equivalence is raised virtually entirely in the context of spliced-DNA crops and foods,¹⁰⁷ except in Canada.¹⁰⁸ Spliced-DNA foods can be tested more readily than, for example, a food derived from a wide genetic cross, because of the superior genetic definition available for the spliced-DNA food. However, logically a crop plant that has only conventional breeding inputs may produce food that is no less deviated from a reference food than its spliced-DNA counterpart and therefore should be subject to similar scrutiny regardless of considerations about how difficult it may be to design appropriate tests. The concept of substantial equivalence is entirely compatible with the notion that the characteristics of gene products and their metabolic consequences, not the means by which the gene was introduced into a cultivar, are material in establishing testing requirements.

Claims that DNA-spliced crops and crop products are “untested” clearly are untrue, and by any measure the testing of transgene crops has been very extensive, especially as compared to the testing of their conventional counterparts. Consider a food introduced into developed regions of the world in the 20th century, the kiwi fruit. This new crop was developed without benefit of DNA splicing or government regulation. Kiwifruit resulted from the efforts of plant breeders eager to create a wholesome and desired product. For kiwifruit, as for many other fruits, as well as nuts and grains, food allergy or food intolerance has been documented

¹⁰⁷ Kuiper, H. A., Kleter, G. A., Noteborn, H. P. J. M. & Kok, E. J. (2001). Assessment of the food safety issues related to genetically modified foods. *Plant Journal* 27, 503-528.

¹⁰⁸ CFIA (2000). Regulatory Directive 2000-07: Guidelines for the Environmental Release of Plants with Novel Traits within Confined Field Trials in Canada <http://www.inspection.gc.ca/english/plaveg/pbo/dir/dir0007e.shtml>. Ottawa, Ontario, Canada: Canadian Food Inspection Agency. Plant Health and Production Division, Plant Biosafety Office.

for a few people.^{109, 110} However, kiwifruit is among fruits recommended for consumption by children to reduce the prevalence of asthma. That is, phenotype testing resulted in a crop that provide numerous benefits and, as is likely to occur in virtually all cases, a risk to at least a few people.

The first new crop to be commercialized from DNA splicing technology was the Flavr Savr tomato of Calgene, Inc. The Flavr Savr tomato bears a transgene designed to reduce the accumulation of a tomato fruit-softening enzyme, polygalacturonase. Data submitted to the U.S. Food and Drug Administration (FDA) by Calgene researchers and regulatory specialists included animal feeding studies showing the new tomato to be indistinguishable in almost every way from the traditional fresh market tomato in respect to carbohydrates, vitamins, minerals, proteins, amino acid composition, alkaloid content, nutrient values. The exceptions were that fruit cell-wall pectin degraded more slowly for the Flavr Savr tomato than for the control tomato, and Flavr Savr tomato paste had a higher viscosity. Both of these outcomes are expected and intended results from decreased accumulation of polygalacturonase.^{111, 112} The Flavr Savr tomato no longer is on the market. Although public acceptance was favorable, costs of production and distribution resulted in losses on each sale and withdrawal of the product from the market. The reduced-polygalacturonase technology had a second life in a processing tomato line whose product was tomato paste sold in the U.K.¹¹³

¹⁰⁹ Fahlbusch, B., Rudeschko, O., Schumann, C., Steurich, F., Henzgen, M., Schlenvoigt, G. & Jaeger, L. (1998). Further characterization of IgE-binding antigens in kiwi, with particular emphasis on glycoprotein allergens. *Journal of Investigational Allergology & Clinical Immunology* 8, 325-332.

¹¹⁰ Kazemi-Shirazi, L., Pauli, G., Purohit, A., Spitzauer, S., Froeschl, R., Hoffmann-Sommergruber, K., Breiteneder, H., Scheiner, O., Kraft, D. & Valenta, R. (2000). Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. *Journal of Allergy and Clinical Immunology* 105, 116-125.

¹¹¹ Redenbaugh, K., et al., *Safety Assessment of Genetically Engineered Fruits and Vegetables. A Case Study of the Flavr Savr™ Tomato*. 1992, Boca Raton, Florida: CRC Press. 267.

¹¹² Martineau, B., *First Fruit*. 2001, New York: McGraw-Hill. 270.

¹¹³ Bruening, G. and J.M. Lyons, *The case of the Flavr Savr tomato*. California Agriculture, 2000. 54(4)(4): p. 6-7.

Other studies comparing the composition of spliced-DNA crop foods with their non-transgenic counterparts also have failed to uncover significant differences.^{114, 115, 116} All of the approximately 40 spliced-DNA crops that have been commercialized have been subjected at least to the FDA's consultative process, which includes attention to the issues of allergenicity, toxicity, and antibiotic resistance.¹¹⁷ Additional scrutiny is provided by the U.S. Department of Agriculture and the U.S. Environmental Protection Agency. In contrast, the testing of conventionally bred crop plants and their products has been less extensive and without regulatory oversight.

FOOD SAFETY ISSUES OF SPECIFIC GENE CONSTRUCTIONS

Although there appears to be no scientific basis for singling out spliced-DNA crops and crop products for special scrutiny and regulation, relative to conventionally bred crops, specific genes introduced into specific plants by any means, not just DNA splicing, might warrant special attention. Progeny from a wide cross between a cultivar and a poisonous wild relative might be examined for the possible presence of those toxins known to be present in the wild relative. There are no regulations in the United States requiring governmental scrutiny of progeny from a cross with a poisonous wild plant, and this report does not advocate such regulation. However, it is important to note that the current regulatory obsession with transgenic crop plants to the exclusion of cultivars genetically improved by other methods likely would not survive a logical prioritization of food safety regulatory efforts. In fact, Canada regulates the introduction

¹¹⁴ Nida, D.L., et al., *Glyphosate-tolerant cotton: The composition of the cottonseed is equivalent to that of conventional cottonseed*. *Journal of Agricultural and Food Chemistry*, 1996. 44: p. 1967-1974.

¹¹⁵ Taylor, N.B., et al., *Compositional analysis of glyphosate-tolerant soybeans treated with glyphosate*. *Journal of Agricultural and Food Chemistry*, 1999. 47: p. 4469-4473.

¹¹⁶ Sidhu et al., 2000. 48: p. 2305 -2312.

¹¹⁷ Thompson, L., *Are bioengineered foods safe?* http://www.fda.gov/fdac/features/2000/100_bio.html. 2000, FDA Consumer magazine.

of new crop plant lines developed by induced mutations and somaclonal variation under the same rules that apply to spliced-DNA crop lines. Thus, Canadian regulations recognize that it is the properties of the specific plant line that are important, not the technology by which the line was derived.¹¹⁸

The issue of the use of antibiotic resistance genes as an adjunct in the process of preparing transgenic plants is considered to be a significant risk under CU point 2. CU point 2 eventually may have historical interest only because selections based on other approaches are available, such as introducing a gene that allows the plant to use a new sugar energy source.¹¹⁹ Nevertheless, it is important to note that the use of antibiotic resistance genes, particularly kanamycin resistance, in crops that were commercially released was allowed only after serious study. CU Point 2 is concerned with a public health issue, the possible development of antibiotic resistant bacteria because of gene transfer from plants bearing a transgene construction that includes an antibiotic selection trait. Kanamycin was a good choice as an antibiotic resistance “marker” for plant transformation because kanamycin rarely now is used in human medicine because of its toxicity and the abundance of bacteria already resistant to this antibiotic. There is no evidence that direct plant-to-microbe DNA transfer can occur. In response to a petition filed by Calgene, Inc., before the Flavr Savr tomato was commercialized, the U.S. Food and Drug Administration (FDA) considered “whether there would be a meaningful increase in antibiotic-resistant pathogenic microbes” due to the transfer of kanamycin resistance genes from plants to microbes.^{120, 121, 122} Based on analysis of worst-case scenarios, the FDA concluded that plant-microbe

transfer of kanamycin resistance would be orders of magnitude below the level needed to have an effect against the background human gut bacteria and soil bacteria that already bear kanamycin resistance genes. The FDA amended the food additive regulations to provide for safe use of kanamycin resistance genes and found that the presence of a kanamycin resistance gene and protein “is not a material fact that must be disclosed in the labeling of foods.”¹²³

Probably the most widely commercialized crop transgenes, in terms of planted acreage, are those conferring tolerance to the herbicide glyphosate. Possible food safety issues associated with spliced-DNA glyphosate tolerance relate both to the transgene and its expressed protein enzyme and to the herbicide glyphosate itself. In feeding studies with dogs, rats, and mice, glyphosate fed at greater than 300 mg per kg of body weight was without observed effect (corresponding to a 110 lb person consuming 15 g (0.5 oz) of glyphosate a day). The EPA tolerance limit for glyphosate in soybean products is 20 ppm (parts-per-million), corresponding to about 0.01 g of glyphosate in a pound of food. The mutant CP4 EPSP-synthase enzyme protein that confers glyphosate tolerance is readily digested in gastric juice. This observation, and the other characteristics of the protein, suggest that CP4 EPSP-synthase is highly unlikely to be a food allergen. No toxic effects of the protein have been detected in feeding and other studies on the CP4 EPSP-synthase. Probably there is no significant food safety issue associated with glyphosate-tolerant crops.

When federal regulators conclude that the properties of a plant line derived by DNA splicing are not significantly different than the properties of the corresponding non-transformed line,

¹¹⁸ CFIA, 2000.

¹¹⁹ Lucca, P., Ye, X. & Potrykus, I. (2001). Effective selection and regeneration of transgenic rice plants with mannose as selective agent. *Molecular Breeding* 7, 43-49.

¹²⁰ FDA (1994). Secondary direct food additives permitted in food for human consumption; food additives permitted in feed and drinking water of animals; aminoglycoside 3'-phosphotransferase II; Final Rule, <http://frwebgate3.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=9715518973+0+0+0&WAISSaction=retrieve>. *Federal Register* 59, 26700.

¹²¹ Nap, J. P., Bijvoet, J. & Stiekema, W. J. (1992). Biosafety of kanamycin-resistant transgenic plants. *Transgenic Research* 1, 239-249.

¹²² Redenbaugh, K., Hiatt, W., Martineau, B., Lindemann, J. & Emlay, D. (1994). Aminoglycoside 3'-phosphotransferase II (APH (3')II): Review of its safety and use in the production of genetically engineered plants. *Food Biotechnology (New York)* 8, 137-165.

¹²³ FDA 1994.

the new plant line may be designated as an “unregulated item” of commerce. Worldwide through 2000, the crop lines that have been approved as unregulated items or otherwise for commercial production, in 20 countries, are represented by 47 combinations from 17 crops species and nine crop traits, derived from 73 transformation events carried out by researchers at 25 companies, universities, and research institutions.¹²⁴

SPECIFIC GENE CONSTRUCTIONS AND ALLERGENICITY; STARLINK™ CORN

CU point 3 correctly states that spliced-DNA transgene products are proteins and that food proteins may cause allergic reactions. However, most foods contain proteins and, of all food proteins, only about 2% pass through the alimentary canal mucosa in a sufficiently intact state to be recognized by the immune system. Of that 2% of proteins remaining partially intact, only a very few proteins cause the great bulk of food allergies. No allergic reaction has been or is likely to be attributed to processes for creating either conventionally bred or spliced-DNA plants. Therefore, the focus must be on specific proteins. The known allergenic proteins for the most part are abundant (>1% of the food mass) proteins of tree nut, legume, seafood, dairy or wheat origin. Proteins that are of low abundance and are rapidly degraded in the stomach are not candidates as food allergens. Developing a food allergy also requires repeated exposure to the allergen. Transgene proteins of spliced-DNA plants are of low abundance in the edible part of the plant, and tests show that almost all are readily degraded in the stomach. As is indicated above, foods from plants that were developed from wide genetic crosses (i.e., conventionally bred plants) have unknown proteins that have not been characterized for their potential allergenicity, but such plants are not subject to regulation.

“StarLink™” corn, with the Cry9C *Bt* insecticidal protein, recently has been in the

¹²⁴ Agbios, *Essential Biosafety CD-ROM*. 2001, Agricultural and Biotechnology Strategies, Inc., www.agbios.com: Merrickville, ON K0G 1N0 Canada.

news because it has been found in human foods. Of about 40 commercialized plant transgene proteins, including other *Bt* proteins, only Cry9C required more than seconds or a few minutes to be digested under conditions found in the stomach. For this reason, StarLink™ corn was approved for animal feed, but not for food use. Most agree that the StarLink™ corn should not have been commercialized unless and until the allergenic potential of Cry9C was found to be negligible, and Aventis CropScience, the developer of StarLink™, voluntarily withdrew its registration. Cry9C does not resemble known allergens. Cry9C is present at 0.013% of StarLink™ corn proteins, and StarLink™ corn is estimated to represent no more than 0.01%, 0.23% and 0.14% of the corn grain in the human food supply in 1998, 1999 and 2000, respectively.¹²⁵ Therefore, even if Cry9C were to be shown to be allergenic, it is almost certain that there has been no significant risk to the public. Aventis CropScience has submitted additional data and is seeking an EPA approval of Cry9C protein in corn for human consumption for a four year period. Although StarLink™ corn is no longer planted, the four year period would allow existing stocks to be consumed and the StarLink™ corn, since it is no longer planted and is not a candidate for re-registration, would no longer be in the food supply.

In collaboration, the Centers for Disease Control and Prevention¹²⁶ and the FDA analyzed serum samples from 17 people who reported, or whose physician reported, symptoms consistent with allergic reaction after consuming corn-containing products that could have been derived from StarLink™ corn. Although immunoglobulin E (IgE) reacting with grass pollen and other common allergens was detected among the serum samples, no serum samples reacted with the

¹²⁵ EPA, *EPA preliminary evaluation of information contained in the October 25, 2000 submission from Aventis CropScience..* 2000, U.S. Environmental Protection Agency: Washington, D.C. p. 26.

¹²⁶ CDC, *Investigation of Human Health Effects Associated with Potential Exposure to Genetically Modified Corn*. <http://www.cdc.gov/nceh/ehhe/Cry9cReport/complete.htm>. 2001, Centers for Disease Control and Prevention: Atlanta, GA. p. 17 + Appendices.

Cry9C *Bt* protein. Most, but not all, food allergies are associated with the development of serum IgE molecules that react with the protein that induces the allergic response. Thus, as expected considering the low and infrequent exposure that anyone reasonably could have to Cry9C protein, the CDC and FDA obtained no evidence for anyone actually developing an allergic reaction to Cry9C protein or StarLink™ corn.

FOOD LABELING FOR SPLICED-DNA CONTENT

Labeling of a food for its spliced-DNA crop origins is a matter of far greater effort and consequence than simply adding a sentence to the food label text. As is indicated below, labeling food for transgene-derived constituents is misleading, costly and not scientifically justified. Labeling for spliced-DNA content also allows activists to target any product so labeled. From 1996 through early 1999, two major grocery chains in the United Kingdom sold more than 1.8 million cans of a tomato paste from DNA-spliced tomatoes grown and processed in California.¹²⁷ The processing tomato was engineered with the same polygalacturonase-reducing gene that was successful in the Flavr Savr tomato. Reduced processing costs, due to lower temperature requirements in an initial heat step, allowed a 20% lower price for the tomato paste. Sales of the paste dropped dramatically in late 1998 during a campaign by activists against DNA-spliced foods that was stimulated by a British Broadcasting Company (BBC) program. The BBC program reported on rat feeding studies purported to conclude that there is a general adverse effect from eating DNA-spliced foods. The corresponding publication on the rat feeding experiments subsequently was discredited and retracted.¹²⁸ However, the grocery chains withdrew the tomato paste from its shelves.

Presumably food labeling should be not only truthful but also limited to material information and information that is not misleading. What is the consumer likely to think when reading a food label that reveals spliced-DNA origins of ingredients?

Presumably the consumer will treat revelations of spliced-DNA crop plant content as being similar to disclosures about calories, calories from fat, cholesterol or sodium, concluding that there must be some reason to limit intake of foods of spliced-DNA plant origin. Information about spliced-DNA content, unlike information about calories, etc., is not material but, as the U.K. experience demonstrates, can be highly influential.

Labeling for spliced-DNA content is likely to be costly. Implementation and enforcement of requirements for labeling as to spliced-DNA origin would be a substantial technical challenge and would impose a significant economic cost. Separate commodity streams, with “identity preservation” would be required. For example, conventional corn and spliced-DNA corn appear to be identical except when examined by highly sophisticated and expensive molecular tests capable of detecting a single gene or a single protein in tens of thousands of genes and proteins. The magnitude of economic costs of labeling is unknown but has been estimated by a major accounting firm to be substantial.¹²⁹ Presumably the additional costs of testing and food manufacturers’ concerns about adverse implications of spliced-DNA labeling would drive many transgene-derived food products from the market, at least in industrialized countries.

If spliced-DNA derived food products represented a general food safety risk perceptibly greater than the general risks of eating any food, labeling a food for GE-origin might be justified. However, no evidence supports an actual food safety issue for spliced-DNA or conventionally bred foods that can be traced to their spliced-DNA or conventionally bred origin. In this context, a comparison of spliced-DNA foods with organic foods and health foods is instructive. Conventional farming, spliced-DNA farming and organic farming all represent technologies for producing safe, wholesome foods, when properly practiced. Virtually everyone in the U.S. has consumed foods derived from spliced-DNA crops. For example, 54% of the U.S. soybean crop in 2000 was planted to

¹²⁷ Bruening and Lyons, 2000. 54(4)(4): p. 6-7.

¹²⁸ U.K. House of Commons, *Scientific advisory system: genetically modified foods*. 1999, U.K House of Commons Select Committee on Science and Technology. <http://www.fern.org/pmhp/dc/genetics/sci-tec.htm>: London.

¹²⁹ KPMG, *KPMG Report on the Compliance Costs Facing Industry and Government Regulators in Relation to Labeling Genetically Modified Foods*; http://www.anzfa.gov.au/documents/gen24_99.asp. 1999, Australia/New Zealand Food Authority (ANZFA).

transgenic lines, and 60% of all processed foods have constituents derived from soybean. Although the market penetration of spliced-DNA crop products is extensive, no associated food safety problems have been documented to be associated specifically with spliced-DNA origin. The products of organic farming have a much smaller market penetration than the products of spliced-DNA crops. Nevertheless, on rare occasions, food safety problems and instances of infections have been specifically associated with the consumption of organic foods and health foods.^{130, 131} Therefore, one would have expected food safety problems specifically associated with food of spliced-DNA origin, if there were any such problems, to have appeared.

A requirement for general labeling of food products for spliced-DNA constituents does not seem to have any scientific basis or utility and, by casting unwarranted suspicion on such products, would reduce the options for improving the quality and quantity of the world's food supply. Labeling for spliced-DNA content also is a disincentive to integrating spliced-DNA technologies and other technologies, including some aspects of organic farming, that can be supportive of more sustainable agriculture. Food safety advantages from spliced-DNA crops¹³² would not be realized, such as a documented reduction in mycotoxin load for corn.¹³³ Only spliced-DNA crop technology is capable of making quantum improvements in food quality,¹³⁴ but labeling for spliced-DNA

content likely would cause these improvements to be underutilized.

FOOD LABELING POLICY

CU point 4 recommends general labeling of transgene-derived foods "in the event that some unexpected difficulty should develop." One could argue that labeling of food for the presence of *specific constituents* might be of assistance in tracing an "unexpected difficulty." However, a requirement for general labeling of foods for spliced-DNA origin clearly would not be of material assistance, since allergens and toxins are substances, not processes. Any concern about an improbable "unexpected difficulty" certainly applies more directly to foods from conventionally bred crops than to foods from spliced-DNA crops, and conventionally bred crop products have been consumed extensively for decades without demonstrated adverse effect attributable to the conventionally bred process. Calls for *general* labeling of all foods for transgenic origin, or other *general* restrictions on the use of crop transgenes, are scientifically no better justified than a call to label or restrict food from crops domesticated after the 19th century or from crops derived from wide genetic crosses or any other non-transgene biotechnology.

Current U.S. Food and Drug Administration (FDA) policy does not require the labeling of foods for spliced-DNA origin. Excerpts from interpretations of U.S. law by officials of the FDA¹³⁵ appear below:

"Consumers must be informed, by appropriate labeling, if a food derived from a new plant variety differs from its traditional counterpart such that the common or usual name no longer applies to the new food, or if a safety or usage issue exists to which consumers must be alerted."

"The agency does not believe that the method of development of a new plant variety {including the use of new techniques}

¹³⁰ Tschaepe, H., et al., *Verotoxinogenic Citrobacter freundii associated with severe gastroenteritis and cases of haemolytic uraemic syndrome in a nursery school: Green butter as the infection source*. *Epidemiology and Infection*, 1995. 114(3): p. 441-450.

¹³¹ Taormina, P.J., L.R. Beuchat, and L. Slutsker, *Infections associated with eating seed sprouts: An international concern*. *Emerging Infectious Diseases*, 1999. 5(5): p. 626-634.

¹³² Betz, Hammond, and Fuchs, 2000. 32(2): p. 156-173.

¹³³ Munkvold, G.P., R.L. Hellmich, and L.G. Rice, *Comparison of fumonisin concentrations in kernels of transgenic Bt maize hybrids and nontransgenic hybrids*. *Plant Disease*, 1999. 83(2): p. 130-138.

¹³⁴ Ye, X., et al., *Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm*. *Science*, 2000. 287: p. 303-305.

¹³⁵ FDA, *Food and Drug Administration. Statement of policy: foods derived from new plant varieties*. *Federal Register*, 1992. 57(104): p. 22984-23001 (<http://vm.cfsan.fda.gov/~lrd/biotechm.html>).

is normally material information within the meaning of 21 USC 321(n) and would not usually be required to be disclosed in labeling for the food.”

FDA authorities clearly distinguish the process by which a food is prepared from its composition. The process used is irrelevant, but the presence of specific substances, regardless of how they were introduced, may be relevant from a food safety perspective and may require labeling. In 1998, an alliance of Greenpeace and other groups opposing spliced-DNA foods filed suit in the U.S. District Court for the District of Columbia, civil action no. 98-1300, seeking to force the FDA to institute additional testing and labeling requirements for foods of spliced-DNA origin. In October 2000, the 1992 FDA policy was upheld, and the suit was dismissed in an opinion rendered by Judge Colleen Kollar-Kotelly. The court noted and gave deference to the FDA’s position that spliced-DNA foods do not “present any different or greater safety concern than foods developed by traditional plant breeding,” and concluded labeling was not warranted.¹³⁶

SPLICED-DNA, FOOD SAFETY, REGULATIONS AND THE “PRECAUTIONARY PRINCIPLE”

Probably the crop DNA transfer experiments with the greatest (but negligible) risk were performed decades ago in the production of conventionally bred crops using induced mutations and wide genetic crosses. We all have safely consumed and continuously benefited from foods derived from the resulting cultivars. As the material presented in this section shows, spliced-DNA technology not only allows the introduction and improvement of genes not possible with the older technologies, but does so with much greater certainty as to the genetic character of the new cultivar. European regulators, nevertheless, have invoked a “precautionary principle” as part of their official regulatory framework for transgenic crops and crop products, but not for conventionally developed crops and crop products.^{137, 138} The quoted text of Marvier¹³⁹ also reflects the “precautionary principle” in the phrase “completely safe.” The precautionary principle requires the party developing a new technology to prove it

is absolutely safe. This, of course, is a standard unattainable in any realm of human endeavor. The application of the precautionary principle, with its strong reliance on hypothesis rather than observations, unfortunately can enhance political intrusion into regulatory processes.

If the precautionary principle had been applied to past efforts at crop introduction and crop improvement, our diets would be considerably less varied. For example, a few people are at great risk to severe allergic reaction if they consume peanuts, but peanuts are not banned from the food supply in part because of the benefits that accrue to the great majority in the population. A VFNT tomato line, bearing tens of unknown genes from a poisonous plant, may have been ruled unnecessarily risky and, if approved, certainly would have required labeling of the fruit and tomato products for their content of unknown *L. peruvianum* genes. Fortunately, because the precautionary principle was not in place, unwarranted restrictions were not imposed on our consumption of the very popular VFNT cherry tomato, peanut butter, and kiwi fruit, among many other crop products.

ACKNOWLEDGMENTS

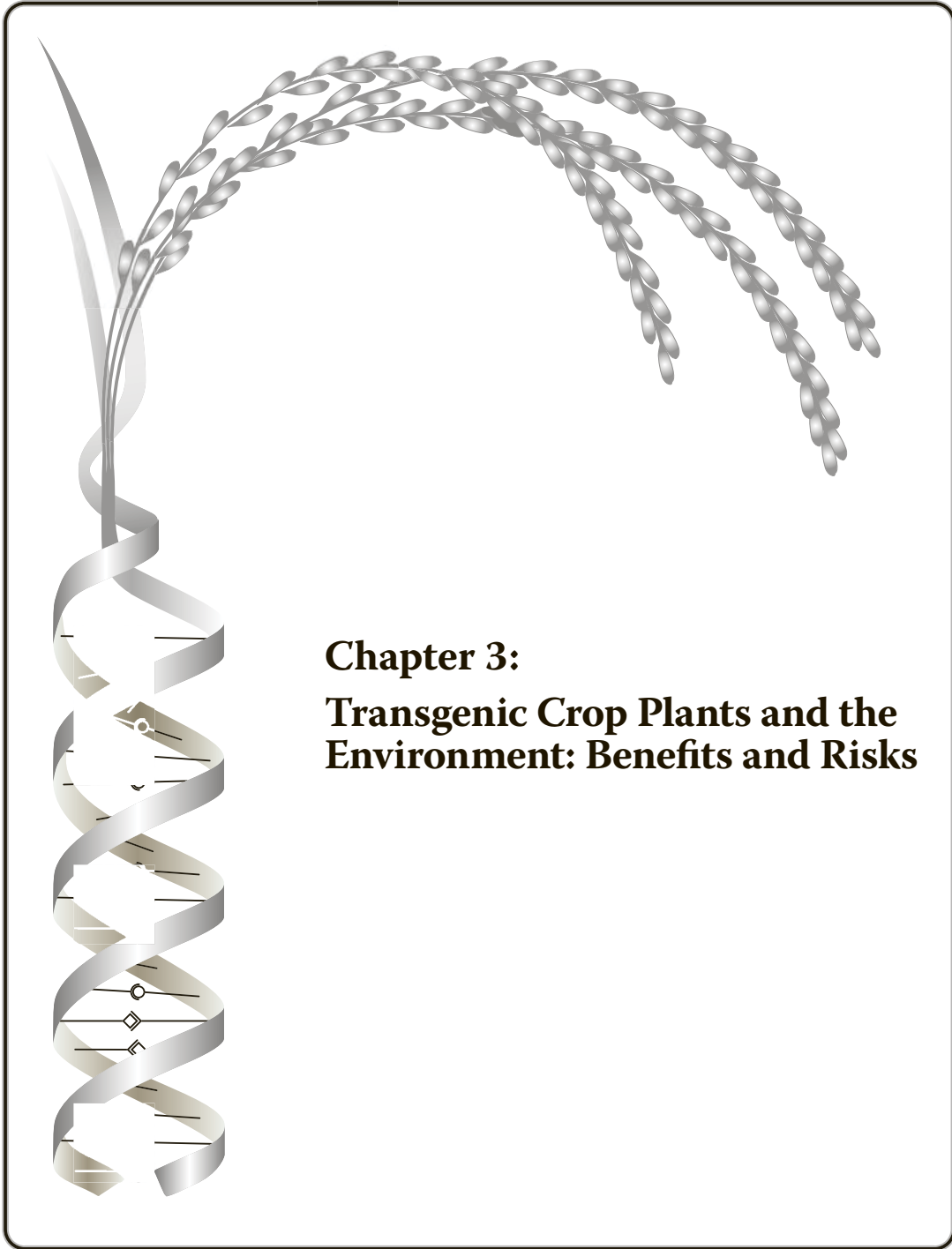
The author is grateful to Keith Redenbaugh, Valerie Williamson, Kevin Fort, Norman Ellstrand, Carl Winter and Cynthia Wagner Weick for providing useful comments on the manuscript.

¹³⁶ Osvath, R., *Federal judge upholds FDA biotech policy*. 2000, FCN Publishing, Food Product Design, A CRC Company, 1725 K St., NW Suite 506, Washington, DC 20006.

¹³⁷ Council of the European Communities, Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms. Community legislation in force, Document 390L0220. http://europa.eu.int/eur-lex/en/lif/dat/1990/en_390L0220.html. Official Journal L, European Economic Community, 1990. 117: p. 0015-0027.

¹³⁸ European Commission, *Communication from the European Commission on the Precautionary Principle*. 2000, Commission of European Communities: Brussels. p. 29.

¹³⁹ Marvier, 2001. 89(2): p. 160-167.



**Chapter 3:
Transgenic Crop Plants and the
Environment: Benefits and Risks**

Chapter 3: Transgenic Crop Plants and the Environment: Benefits and Risks

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INTRODUCTION

Technological innovations bring their own set of benefits and risks to the environment, and no technology is 100% safe. The same is true both for transgenic crop plants that contain novel traits incorporated by the tools of biotechnology and for crop cultivars produced by traditional plant breeding methods. The majority of traditional plant breeding methods accomplish gene transfer between plants by sexual reproduction where pollen of one plant fertilizes the egg cell of another plant; therefore, only closely related plants can be used to exchange genes. But transgenic plants can be genetically modified to contain traits from either related or unrelated organisms. Transgenic technology refers to sophisticated techniques capable of transferring genes from donor organisms to recipient organisms without the involvement of sexual reproduction between them. Also, plant scientists can move genes from any source – plants, animals, or bacteria – into almost any crop.¹⁴⁰

Both traditional plant breeding methods and transgenic techniques create new gene combinations with novel traits such as resistance to pests, diseases, and herbicides. Although both types of techniques generate a similar end product, that is, crop plants with certain novel traits, there may be large qualitative differences in the degree of “genetic novelty” brought into transgenic plants compared to traditional cultivars. For example, almost all traditionally improved varieties of corn are the result of the interbreeding of corn varieties. In contrast, transgenic corn may contain transgenes from an organism as closely related as the same species or as distantly related as a bacterium. For example, “*Bt* corn” contains a gene from soil bacterium, *Bacillus thuringiensis*. The bacterial gene is capable of producing a class of proteins called “Cry” proteins, and each one of these proteins is toxic to a specific group of insects.

¹⁴⁰ Rissler, J. and M. Mellon. 1996. *The ecological risks of engineered crops*. The MIT Press, Cambridge.

Bt crop plants are engineered to contain Cry protein genes from the bacteria, and accordingly, each *Bt* cultivar is capable of producing the same toxic protein against a specific group of insect species. Thus transgenic crop plants hold great promise for the world agriculture, as novel insect-resistant crop plants such as *Bt* corn could not have been generated by traditional plant breeding methods. However, these novel transgenic plants may also bring a set of new problems to the environment, since such transgenic plant genotypes have never previously occurred in the environment before. One of the reasonable steps after the creation of a transgenic product, therefore, is to evaluate its potential benefits and risks to the environment.

The most important criterion in the risk-benefit analysis of impacts of transgenic crop plants on the environment is that the risks or benefits should be compared to conventional agricultural practices.¹⁴¹ Certain types of risk or benefits of impact of transgenic plants on the environment are relatively simple to estimate. A new insect-resistant transgenic soybean may require little or no insecticide application, benefiting the environment in terms of reduced chemical toxicity in the soil and water. But the same transgenic insect-resistant soybean cultivar may create a hazard if it poisons a beneficial insect in the environment. Therefore, to estimate the true environmental benefits of using transgenic plants, it is necessary to evaluate the costs and benefits of alternative decisions – there may be environmental benefits obtained by forgoing the cultivation of transgenic plants, or there may be costs to the environment in terms of benefits forgone.

¹⁴¹ Cook, R. J. 1999. *Science-based risk assessment for the approval and use of plants in agricultural and other environments*. pp. 123-130. In, G. J. Persley and M. M. Lantin (ed.) *Agricultural Biotechnology and the Poor*. Proceedings of an International Conference, 21-22 October 1999. Consultative Group on International Agricultural Research, Washington, D.C.

Conventional risk-benefit analysis involves putting a monetary value to such benefit and risk factors,¹⁴² but some environmental impacts of transgenic cultivars are difficult to quantify because the natural environment is a complex entity. It is possible to estimate the amount of reduced use of a chemical pesticide in the environment by the introduction of a new transgenic insect-resistant soybean cultivar, yet it is difficult to quantify several other collateral positive or negative impacts that might occur, for example, to soil microorganisms or to other non-target organisms. Therefore, while discussing benefits of transgenic crops on the environment, in this review we placed more emphasis on those benefits that are tractable for economic analysis, but we caution the reader to recognize that the review is necessarily incomplete for lack of data.

Like transgenic benefit analysis, transgenic risk analysis has to consider many subtle factors. Risk is a combination of a hazard and exposure. A hazard is a potential adverse effect from the proposed activity. The existence of a hazard does not imply significant danger from the activity, because the hazard might have very low probability of occurrence, i.e., the exposure is low. For example, smoking is a health hazard because of the risk of lung cancer increases with increased exposure to smoke. In other words, occasional smoking (hazard) may not bring any risk (lung cancer) to a smoker because the potential for getting lung cancer depends upon the lung's exposure to duration and intensity of smoke. Therefore, the most fundamental component of risk analysis is hazard identification. But the issue of exposure makes obvious the fact that the realization of risks is delayed relative to the introduction of hazards and may be difficult to detect.

An ideal risk-benefit analysis of transgenic crop plants would involve comparing the transgenic crops' risks and benefits with crops cultivated under as agriculture systems as possible, including organic and sustainable agriculture.¹⁴³ We did not find any peer-reviewed research reports directly comparing

transgenic crop plants with crops grown under sustainable agriculture system. Therefore, all the transgenic risk-benefit analyses presented in our report are mainly from the comparisons made on conventional crop plants. Furthermore, the few risk-benefit analyses of impacts of transgenic plants on the environment conducted so far are very tentative, requiring more data to draw definitive conclusions. In other words, "neither the benefits nor the risks of transgenic plants are certain or universal...and may vary on a case-by-case basis."¹⁴⁴ In the following section, we categorize the major benefits and risks of transgenic plants on the environment. Then we consider whether California, a state that stands out in both its agricultural and environmental resources, is apt to experience the same benefits and risks of transgenic plants as the rest of the country.

BENEFITS

Four general categories of potential environmental benefits from release of transgenic crop plants have been identified: 1) indirect environmental benefits accrued from the direct economic benefits of higher crop yields; 2) reduced chemical toxicity in the environment due to pest-resistant cultivars; 3) efficient use of renewable resources such as land, water, and soil nutrients; and 4) accurate monitoring of environmental pollution using pollution-sensitive transgenic plants.

Indirect Benefits from Increased Yield

In the last century, more land has been brought under cultivation than any of the preceding centuries to meet the food demand of a growing human population, and the growing food demand has remained one of the major environmental threats.¹⁴⁵ Plant breeding techniques that help to produce more food from a given piece of land may reduce the rate of spread of cultivation to areas not

¹⁴² Abelson, P. 1979. *Cost benefit analysis and environmental problems*. Saxon House, Westmead, England.

¹⁴³ NRC (National Research Council). 2000. *Genetically Modified Pest-Protected Plants: Science and Regulation*. National Academy Press, Washington, D.C.

¹⁴⁴ Wolfenbarger, L. L., and P. R. Phifer. 2000. *The ecological risks and benefits of genetically engineered plants*. *Science* 290:2088-2093.

¹⁴⁵ Clout, H. 1999. History of world agriculture: From neolithic times to the contemporary crisis, *J. Rural Agric.* 15: 227.

presently under cultivation, or may gradually free up areas presently under cultivation. Thus, crop yield improvement can act as an indirect benefit to the environment. The majority of the transgenic crops under cultivation have been developed to resist pest damage or to resist herbicide chemicals that are sprayed to kill crop weeds. Although the pesticide- and herbicide-resistant crops were not specifically developed to improve yield, reduced pest and weed damage on crop plants have resulted in higher yield in certain cases.

The Economic Research Survey of the United States Department of Agriculture¹⁴⁶ reported that, since their introduction, *Bt* cotton and *Bt* corn resulted in significantly higher yields in most years in certain areas of the United States. According to this survey, from 1996 to 1998 the average annual yield of *Bt* cotton in three regions of the U.S. outpaced yields of conventional cotton by nine to 26% in four of nine cases studied, but were not significantly different in three cases, and were slightly lower in the remaining two cases.¹⁴⁷ Such differences in yield performance were attributed to variation in the pest damage across the regions. Despite such differences in yield data, a general trend in yield improvement is emerging from *Bt* cotton in the U.S. For example, in 1995 all cotton cultivars grown in the United States were nontransgenic, and the average crop loss to tobacco budworm and cotton bollworm was around 4% with the loss reaching 29% in Alabama. Three years later, in 1998, the *Bt* cotton accounted for 17% of the total cotton crop and over 90% of the cotton crop in Alabama. That year, because of reduced insect damage due to the transgenic cotton, farmers harvested 85 million extra pounds of lint with an estimated benefit of more than \$92 million.¹⁴⁸

¹⁴⁶ USDA (ERS). 1999. *Genetically engineered crops for pest management*. (<http://www.ers.usda.gov/whatsnew/issues/gmo/index.htm>).

¹⁴⁷ Klotz-Ingram, C., S. Jands, J. Fernandez-Cornejo, and W. McBride. 1999. *Farm level production effects related to the adoption of genetically modified cotton for pest management*. *AgBioForum* 2:24-32. (<http://www.agbioforum.org/archives.htm>)

¹⁴⁸ Gianessi, L. P., and J. E. Carpenter. 1999. *Agriculture biotechnology: insect control benefits*. National Center for Food and Agricultural Policy. Washington, D.C.

Yield increases for *Bt* corn have not been as dramatic as those of *Bt* cotton, probably due to the great year-to-year variation in the crop damage by the primary corn pest, European corn borer. It is estimated that, depending on the intensity of this pest damage, the corn yield losses fluctuated widely from 33 to 300 million bushels per year.¹⁴⁹ In 1997, *Bt* protected corn was planted on 4 million acres, and European corn borer infestation was typical to heavy. That year, *Bt* corn provided a yield premium of almost 12 bushels per acre compared to non-*Bt* corn. One year later, European corn borer infestation was extremely light and *Bt* protected corn was planted on 14 million acres. Yet, U.S. farmers that planted *Bt* corn still realized a yield increase of 4.3 bushels per acre compared to non-*Bt* corn.¹⁵⁰ Overall, the general trend in yield increase in *Bt* cotton has been observed across the globe.^{151, 152} The data on *Bt* corn are inconclusive and controversial because whether or not yield gains have occurred depend on the analysis.^{153, 154, 155}

But insect resistant transgenes do not necessarily result in higher yields in other crops. For example, in potato, the *Bt* transgene did not result in any appreciable yield improvement because the majority of insect pests of potato are not vulnerable to the toxin created by the

¹⁴⁹ USDA (APHIS). 1975. *Animal and Plant Health Inspection Service, Cooperative Economic Insect Report*, Vol 25, No. 32.

¹⁵⁰ Carpenter, J. E. 2001. *Case studies in benefits and risks of agricultural biotechnology: Roundup Ready soybeans and Bt field corn*. National Center for Food and Agricultural Policy: Washington, D.C.

¹⁵¹ James, C. 1999. *Preview – global review of commercialized transgenic crops: 1999*. ISAAA Briefs no. 12. ISAAA, Ithaca, NY.

¹⁵² Falck-Zepeda, J. B., G. Traxler, and R. G. Nelson. 1999. *Rent creation and distribution from biotechnology innovations: The case of Bt cotton and herbicide-tolerant soybeans in 1997*, ISAAA Briefs No. 14. ISAAA, Ithaca, NY. (www.biotech.iastate.edu/Bioethics/gmosethics/USDA.pdf)

¹⁵³ James, Preview – global review of commercialized transgenic crops: 1999.

¹⁵⁴ Falck-Zepeda et al, *Rent creation and distribution from biotechnology innovations: The case of Bt cotton and herbicide-tolerant soybeans in 1997*.

¹⁵⁵ www.ucsus.org/food/bt_ren_app3.pdf

Bt transgene.¹⁵⁶ In other words, the extent of economic gain by transgenic crops depends upon the effectiveness of these transgenes in controlling pest damage. There are several other transgenic pest-resistant crops for which field data are not yet available for determining whether they enjoy yield benefits.

Although yield improvement has been the primary focus of traditional plant breeding, the primary objective behind the development of *Bt* cotton or *Bt* corn was to control insect damage to these crops. Any yield gain realized via such pest-resistant transgenic plants is an indirect benefit to the environment, especially in the developing countries. In those countries, particularly the ones with burgeoning populations, where the demand to grow more food is pushing crop production resources to their limits,¹⁵⁷ yield improvement may help to delay their conversion of wildlands to agriculture. It is conceivable that any substantial gain in the crop yield may reduce the stress on arable land in both developed and developing nations. However, no data are available as to whether increased yield due to transgenic traits has actually translated into reduced stress on wildlands. In fact, we are also not aware of whether yield increases accrued from traditional improvement techniques have resulted in reduced land use of natural ecosystems.

Reducing Toxic Chemicals in the Environment

In terms of the number of transgenic plants developed and area under transgenic plant cultivation, there are more pest-resistant transgenic crop plants than any other type.¹⁵⁸ The reduction in use of chemicals for pest control is the most frequent environmental benefit cited of transgenic crop plants.

Every year U.S. farmers apply 971 million pounds of pesticides, mostly to kill insects, weeds, and fungi in their crops. These chemicals may enter the air, soil, ground water, and aquatic

ecosystems, sometimes poisoning wildlife.¹⁵⁹ The transgenic pest-resistant cultivars should theoretically reduce such environmental damage because these transgenic resistant plant cultivars provide their own disease- and insect-defense mechanisms, eliminating, or reducing the need for extensive chemical sprays. Today, most transgenic crops – mainly soybean, corn, cotton, and canola – contain genes enabling them to either resist insect pests or tolerate weed-killing herbicides.¹⁶⁰ Of the crops carrying *Bt* genes, cotton has had the biggest drop in pesticide use.¹⁶¹ Plantings of *Bt* protected cotton in 1996 helped Alabama growers use the least amount of insecticide on cotton since the 1940s.¹⁶² Nationally, the amount of insecticide applied to *Bt* cotton crops in 1997 to control major cotton pests decreased more than 50% compared to non-*Bt* cotton.¹⁶³

In Australia, from 1998 to 1999, relative to conventional cotton, *Bt* cotton received an average of 34% less chemical insecticide or around eight fewer insecticide sprays. Similarly, a four-year analysis of insecticide use on *Bt* cotton in China showed an average of 60 to 80% reduction in chemical insecticide use on *Bt* cotton compared to that applied on conventional cultivars.¹⁶⁴

Besides a significant reduction in the quantity of pesticide used on *Bt* cotton, there was also an overall reduction in the number

¹⁵⁶ Gianessi and Carpenter, *Agriculture biotechnology: insect control benefits*.

¹⁵⁷ Alexandratos, N. 1999. World food and agriculture: Outlook for the medium and longer term. Proc. Natl. Acad. Sci. (USA) 96:5908-5914.

¹⁵⁸ Brown, K. 2001. *Seeds of concern*. Scientific American 284:52-57.

¹⁵⁹ Brown, 52-57.

¹⁶⁰ Brown, 52-57.

¹⁶¹ Betz, F. S., B. G. Hammond, and R. L. Fuchs. 2000. *Safety and advantages of Bacillus thuringiensis-protected plants to control insect pests*. Regulatory Toxicology and Pharmacology 32:156-173.

¹⁶² Smith, R. H. 1997. *An extension entomologist's 1996 observations of Bollgard Bt technology*. In, Proceedings - Beltwide Cotton Conferences. New Orleans, LA. 7-10 Jan, 1997. Cotton Council of America, Memphis, TN. (www.cotton.org/beltwide/)

¹⁶³ USDA (ERS). *Genetically engineered crops for pest management*.

¹⁶⁴ Xia, J.Y., J. J. Cui, L. H. Ma, S. X. Dong, and X. F. Cui. 1999. *The role of transgenic Bt cotton in integrated insect pest management*. Acta Gossypii Sim. 11:57-64.

of pesticide ‘applications’ on *Bt* cotton in the U.S. An application is the number of different active ingredients applied per acre times the number of repeat applications, and differs from the number of trips the sprayer makes over the field. For example, one trip across the field to apply two active ingredients is treated as two applications.¹⁶⁵

Farmers in six major cotton-growing areas of the United States (Alabama, Arizona, Florida, Georgia, Louisiana, and Mississippi) used about six insecticide treatments for tobacco budworm and cotton bollworm in 1995, the year before the introduction of *Bt* cotton. During the next three years in which *Bt* protected cotton was planted, the number of insecticide treatments dropped to an average of two applications.¹⁶⁶ Insecticide treatments on *Bt* cotton did not drop to zero because control was necessary for those insect pests not affected by *Bt* toxin.¹⁶⁷

The reduction in insecticide application in U.S.-grown *Bt* corn is not as dramatic as that for *Bt* cotton. This difference has been attributed to the unpredictable year-to-year fluctuations in the major corn pest, European corn borer. Because of those fluctuations, farmers do not regularly apply insecticide to their corn crops, even before the introduction of *Bt* corn. It was estimated that in 1998 about 5% less insecticide was applied to *Bt* corn than non-*Bt* corn;¹⁶⁸ however, a recent EPA study¹⁶⁹ did not find similar benefit of reduced pesticide usage on *Bt* corn. In other crops such as potatoes, there was a marginal reduction in pesticide usage, partly

because those plants normally require fewer pesticides and have an unpredictable number of pests. Although, so far, there appears to be a significant benefit to the environment from transgenic pest-resistant cotton, it is too early to predict the overall benefit of pest-resistant transgenic crops on the environment because there are a variety of other pest problems for which transgenic cultivars are not commercially available and for which chemical control is still the only option.

Renewable Resources

The intensive agricultural practices during the latter half of the 20th century resulted in accelerated loss of physical and biological qualities of the farm soil.¹⁷⁰ Extensive tillage for controlling weeds and preparing seedbeds induces soil erosion, kills earthworms, and reduces soil microorganisms. According to one estimate, soil erosion in conventional, industrial agriculture can occur 100 times faster than the soil formation rate.¹⁷¹ Rapid soil erosion resulted in about 30% of agricultural soils in the U.S. unsuitable for cultivation.¹⁷² Low tillage systems have been used for many years in traditional communities. Low or no-till agricultural practices do not disturb the soil except during planting,¹⁷³ and weed control is primarily achieved through herbicide treatment.

No-till agriculture in the U.S. has resulted in a number of economic and environmental benefits for U.S. farmers,¹⁷⁴ and no-till methods are gaining popularity in the U.S. For example,

¹⁶⁵ Carpenter, *Case studies in benefits and risks of agricultural biotechnology: Roundup Ready soybeans and Bt field corn*.

¹⁶⁶ Williams, M. R. 1999. *Cotton crop losses*. (<http://www.msstate.edu/Entomology/CTNLOSS/1998loss.html>.)

¹⁶⁷ Betz et al. 32:156-173.

¹⁶⁸ Carpenter, *Case studies in benefits and risks of agricultural biotechnology: Roundup Ready soybeans and Bt field corn*.

¹⁶⁹ EPA. 2001. *Bt Plant-Incorporated Protectants* October 15, 2001 Biopesticides Registration Action Document. (www.epa.gov/oppbppd1/biopesticides/otherdocs/bt_brad2/5%20benefits.pdf)

¹⁷⁰ Herdt, R. W., and R. A. Steiner. 1995. *Agricultural sustainability: Concepts and conundrums*. In, Barnett,

V., Payne, R., Steiner, R. (eds) *Agricultural Sustainability: Economic, Environmental and Statistical Considerations*. Wiley, Chichester, UK.

¹⁷¹ NRC (National Research Council). 1989. *Committee on the Role of Alternative Farming Methods in Modern Production Agriculture*. National Academy Press, Washington, D.C.

¹⁷² Pimentel, D., C. Harvey, P. Resosudarmo, K. Sinclair, D. Kurz, M. McNair, S. Crist, L. Shpritz, L. Fitton, R. Saffouri, R. Blair. 1995. *Environmental and economic costs of soil erosion and conservation benefits*. *Science* 267:1117-1123.

¹⁷³ Conservation Technology Information Center. 1997. *National Crop Residue Management Survey – 1997 Survey Results*. West Lafayette, IN.

¹⁷⁴ Zero Tillage Farmers Association. 1997. *Advancing the Art*. Zero Tillage Farmers Association, Bismarck, ND.

between 1989 and 1997 the use of no-till has increased from 5.1 to 15.6% of total planted acreage in the production agriculture in the U.S.¹⁷⁵ For crops like corn and soybeans, the no-till farming has been gaining popularity covering about 18% of corn and 31% of soybean acreage in a single growing season in the U.S.¹⁷⁶ It is possible that the increase in no-till acreage for corn and soybean during the last decade is due in part to the cultivation of transgenic herbicide-resistant corn and soybean cultivars, but no empirical evidence exists as to how transgenic crops affected soil tillage during this period of time.¹⁷⁷

There is a need to develop crops that thrive under reduced tillage. Resistance to root diseases currently controlled by tillage is particularly important. So also the development of herbicides that can be used as a substitute for weed control by tillage.¹⁷⁸ Herbicide resistant crops have been predicted to improve the soil structure by reducing the need for frequent tillage.¹⁷⁹ We are not aware of any peer-reviewed report addressing whether soil quality has been improved by cultivation of transgenic herbicide resistant plants.

ENVIRONMENTAL MONITORING AND REMEDIATION

Transgenic plants have been proposed as a tool to detect and deal with environmental pollution. Plants are already used to detect pollution.¹⁸⁰ Transgenic

plants can be created with genetic elements leading to pollutant-induced expression of stress proteins that can be fused with gene encoding proteins normally present in the organism of interest and for which simple detection techniques are available. The resulting organisms sense specific changes in the environment and provide responses that can be easily recorded with simple tools. In a laboratory test using transgenic tobacco plants it has been shown that plants can monitor metals and temperature effects in the environment.¹⁸¹ These transgenic plants may be sensitive enough that their responses are triggered at biologically significant levels of contamination.¹⁸² To our knowledge, these transgenic plants have not yet been released for use. Further studies are needed to determine whether transgenic biomarkers are sufficiently cost-effective and sensitive tools for widespread use in environmental monitoring.

In the future, transgenic plants may be grown for “phytoremediation”, to remove or detoxify pollutants in soil. The environmental benefits of such plants might not be as straightforward as they would first appear. For example, mercury contamination of soils is a persistent pollution problem. Plants have already been transformed to mitigate this problem. One approach is to convert highly toxic organic mercury in the soil into less toxic elemental mercury. However, elemental mercury is volatile and can be translocated atmospherically; ultimately precipitation containing mercury could do environmental damage.¹⁸³ A better approach is to create plants that accumulate mercury in their tissues,¹⁸⁴ where it can be harvested, extracted, or disposed of more safely. These “phytoextraction” plants are already capable of accumulating more than one percent of their biomass as mercury, and crop improvement techniques, including genetic engineering, may be able to increase that fraction.

¹⁷⁵ Conservation Technology Information Center. 1997. *National Crop Residue Management Survey – 1997 Survey Results*.

¹⁷⁶ Conservation for Agriculture’s Future. 2001. (www.ctrp.purdue.edu/Core4/CT/ctsurvey/2000/2000USSummary.html)

¹⁷⁷ Winrock International. 2000. *Transgenic crops: An environmental assessment*. Henry A. Wallace Center for Agricultural and Environmental Policy at Winrock International. (<http://www.winrock.org/Transgenic.pdf>)

¹⁷⁸ Powell, G. E., and K. A. Renner. 1999. Weed control in navy bean in reduced tillage systems. *Prod. Agric.* 12:428-433.

¹⁷⁹ Cannell, R. Q., and J. D. Hawes. 1994. Trends in tillage practices in relation to sustainable crop production with special reference to temperate climates. *Soil and Tillage Research*. 30:245-282.

¹⁸⁰ Monciardini, P., D. Podini, and N. Marmioli. 1998. *Exotic gene expression in transgenic plants as a tool for monitoring environmental pollution*. *Chemosphere* 37: 2761-2772.

¹⁸¹ Monciardini et al, 37:2761-2772.

¹⁸² Monciardini et al, 37:2761-2772.

¹⁸³ Pilon-Smits, E; M. Pilon. 2000. *Breeding mercury-breathing plants for environmental cleanup*. *Trends in Plant Science* 5:235-236.

¹⁸⁴ Raskin, I. 1996. *Plant genetic engineering may help with environmental cleanup - commentary*. *Proc. Natl. Acad. Sci. (USA)* 93:3164-3166.

Environmental impacts of these mitigation strategies may be scale-dependent. If the total amount of volatile mercury created is small, it will probably have little environmental consequence. Thus, small-scale use of plants that volatilize mercury could be environmentally beneficial. But, if the scale of volatilization is so large that large amounts of mercury are volatilized, atmospheric mercury levels may rise at regional or larger spatial scales. Atmospheric mercury is returned to ecosystems in precipitation as rain or snow, often far from its source. Once deposited, it is converted into more toxic forms. Deposition of atmospheric mercury released by burning of fossil fuel and medical waste has been identified as a potentially serious environmental problem.^{185, 186} Thus, large-scale phytoremediation based on volatilization may exacerbate what is already a serious concern. Phytoremediation based on phytoextraction would not release elemental mercury into the environment. This strategy might have the additional benefit of potential harvest for the commercialized extraction of mercury. To our knowledge, transgenic plants for phytoremediation have not yet been released for use.

RISKS

The potential environmental risks of transgenic plants are the same categories as those of conventional crop plants.^{187, 188, 189} But, of course, any new crop variety, transgenic or not, may pose risks unique to that variety.¹⁹⁰ While the risks are few, they also may be difficult to detect compared to their environmental benefits. Many types of risks take several years to occur at a level that can be detected using current technologies. Thus, the environmental risks of plants, regardless of the method of modification or whether or not they have been genetically modified, have an extended lag

period delaying their impact on the environment. Because transgenic crops have only been grown commercially for such a short time, the data are not yet available as to whether, or how frequently these risks will be realized. Nonetheless, examples from traditionally improved crops suggest that the risks are indeed real and that if steps are not taken to prevent them, they should occasionally occur for transgenic crops as well. As pointed out in the beginning of the article, any potential risk of crop transgenes should be evaluated taking into consideration the traditional agricultural practices. Furthermore, in this chapter, we present the potential risks that have been discussed about transgenic crops. The issue of risk management is beyond the scope of this chapter.

Five categories of risks from the release of transgenic crop plants have been identified: 1) risks associated with the transgene's movement into a different organism or species and its subsequent expression in that organism; 2) risks associated directly or indirectly with the transgenic plant as a whole; 3) non-target risks associated with the transgene product outside of the plant; 4) risks associated with increased use of herbicides; and 5) resistance evolution in the targeted pests.

Risks Associated with the Movement of Genes

The movement of transgenes does not, in itself, constitute a risk,¹⁹¹ but it can serve as an opportunity for unintentional spread of transgenes in the environment. The movement of transgenes constitutes the "exposure" component of a risk, if a specific hazard is associated with that

¹⁸⁵ Jackson, T. A. 1997. *Long-range atmospheric transport of mercury to ecosystems, and the importance of anthropogenic emissions: A critical review and evaluation of the published evidence*. *Environmental Reviews* 5:99-120.

¹⁸⁶ MacDonald, J. F. 1993. *Agricultural biotechnology: a public conversation about risk*. Ithaca: National Agricultural Biotechnology Council.

¹⁸⁷ NRC. *Committee on the Role of Alternative Farming Methods in Modern Production Agriculture*.

¹⁸⁸ NRC. *Genetically Modified Pest-Protected Plants: Science and Regulation*.

¹⁸⁹ NRC (National Research Council). 2002. *Environmental Effects of Transgenic Plants*. National Academy Press, Washington, D.C.

¹⁹⁰ NRC, *Environmental Effects of Transgenic Plants*.

¹⁹¹ NRC (National Research Council). 1987. *Introduction of recombinant DNA-engineered organisms into the environment: Key issues*. National Academy Press, Washington, D.C.

spread.¹⁹² The spread of transgenes is facilitated by one of three mechanisms, horizontal transfer, seed dispersal, or pollen dispersal, that may move transgenes beyond the point of intentional release and into environments and organisms other than those intended.

Horizontal transfer is the nonsexual transfer of genetic material from one organism into the genome of another.¹⁹³ For example, some plants appear to have occasionally acquired genes from other kingdoms of organisms, such as bacteria.¹⁹⁴ Mechanisms for horizontal transfer are poorly understood. The transfer rate is extremely low compared to within-species gene transfer, but surprisingly high over evolutionary time. For example, flowering plants have apparently horizontally acquired a certain mitochondrial gene from fungi hundreds of times over the last 100 million years.¹⁹⁵ Horizontal transfer is essentially natural genetic engineering. As a risk, horizontal transfer is largely discussed as a source of unanticipated effects. Presently, no data have been published to suggest that the extremely low rate of natural horizontal transfer should be higher or lower for transgenic organisms. Further research in this area could change the assessment and significance of risk.¹⁹⁶

Seed dispersal can occur by unintentional spilling of seed either during the transport

processes that bring seed to the field to be planted or take harvested seed from the field to market.¹⁹⁷ For example, in the United Kingdom, some roadside feral, conventionally bred oilseed rape populations (*Brassica napus*) are apparently constantly replenished by seed spilling from vehicles on their way to a major oilseed crushing plant.¹⁹⁸ In some parts of France, such populations have permanently established as roadside weeds.¹⁹⁹

Dispersal of seeds can also occur directly from crops into the surrounding environment. For example, the majority of the legumes disperse their seeds by way of naturally splitting the pods and ejecting the seeds as far as two to three meters from the mother plant. Animal-, wind-, and water-dispersed fruits are even more efficient in dispersing the seeds as these dispersal mechanisms can carry at least a few seeds several kilometers away from the mother plants.²⁰⁰ Risks usually associated with seed dispersal for transgenic plants are the evolution of increased weediness of the transgenic crop itself and the unintentional contamination of related transgenic or non-transgenic crops. These two types of hazards are discussed in the sections below.

Pollen dispersal provides an opportunity for sexual transfer of crop genes to relatives of the crop, including other varieties of that crop, related crops, and wild relatives.²⁰¹ Specific pollen vectors vary with the crop. Wind and insects are the most frequent agents that carry pollen between plants. Almost all crops, whether largely outcrossing or mostly self-fertilizing, are expected to disperse some pollen. For example, bread wheat is highly self-fertilizing, but is capable of mating

¹⁹² Nickson, T. E. 2001. *The role of communication in ecological assessments of genetically modified crops*. In, K. Ammann, Y. Jacot, G. Simonsen, G. Kjellsson (ed.) *Methods for Risk Assessment of Transgenic Plants*. Volume IV. Birkhauser, Basel, Switzerland. (In press)

¹⁹³ NRC, *Environmental Effects of Transgenic Plants*.

¹⁹⁴ Adams, K. L., M. J. Clements, and J. C. Vaughn. 1998. *The Peperomia cox I group I intron: Timing of horizontal transfer and subsequent evolution of the intron*. *J. Mol. Evol.* 46:689-696.

¹⁹⁵ Palmer, J. D., K. L. Adams, Y. Cho, C. L. Parkinson, Y.-L. Qiu, and K. Song. 2000. *Dynamic evolution of plant mitochondrial genomes: mobile genes and introns and highly variable mutation rates*. pp. 35-57. In, F. J. Ayala, M. W. Fitch, and M.T. Clegg (ed.) *Variation and evolution in plants and microorganisms: toward a new synthesis 50 years after Stebbins*. National Academy Press, Washington, D.C.

¹⁹⁶ Rissler and Mellon. *The ecological risks of engineered crops*.

¹⁹⁷ NRC, *Environmental Effects of Transgenic Plants*.

¹⁹⁸ Crawley, M. J., and S. L. Brown. 1995. *Seed limitation and the dynamics of oilseed rape on the M25 motorway*. *Proc. Royal Soc. London Series B* 259:49-54.

¹⁹⁹ Pessel, F. D., J. Lecomte, V. Emeriau, M. Krouti, A. Messean, P. H. Gouyon. 2001. *Persistence of oilseed rape (Brassica napus L.) outside of cultivated fields*. *Theor. Appl. Genet.* 102:841-846.

²⁰⁰ van der Pijl, L. 1982. *Principles of Dispersal in Higher Plants*. Springer-Verlag, Berlin.

²⁰¹ NRC, *Environmental Effects of Transgenic Plants*.

with plants many meters away.²⁰² Furthermore, although certain crops are typically harvested before flowering (e.g., sugar beet), occasional plants flower prematurely (e.g., “bolters”)²⁰³ or are missed by harvesting equipment and eventually flower. Only a very few crops are apparently 100% male-sterile, producing no pollen (e.g., certain potato varieties, certain ornamentals).

The most publicized risk associated with pollen dispersal from transgenics is the evolution of increased weediness as a result of the sexual transfer of crop alleles to wild relatives.^{204, 205, 206} When wild relatives grow near related crops, it is not unusual for natural hybridization to occur.²⁰⁷ Spontaneous hybridization between crops and their wild relatives has already led to the evolution of difficult weeds, such as weed beets in Europe^{208, 209} and weed rye in California.^{210, 211} One could imagine that certain crop genes that confer pest resistance or otherwise increase plant fitness may potentially contribute to the evolution of increased weediness, especially if these genes escape to a plant that is already a weed (for example, the noxious weed johnsongrass is a close relative of the crop plant sorghum).

A second hazard associated with pollen dispersal is that a common species can overwhelm those that are locally rare with their pollen, increasing the risk of extinction by hybridization in one of two, not

necessarily exclusive ways.²¹² The fraction of hybrids produced by the rare population may be so high that the population becomes genetically absorbed into the common species (genetic assimilation). Also, hybrids may be reduced in fitness (outbreeding depression), and therefore the rare species may be unable to maintain itself. Extinction by hybridization has been long recognized as a conservation problem for animals,²¹³ but has only recently received attention for plants.^{214, 215, 216} Nonetheless, theoretical models have demonstrated the process can be rapid, resulting in local extinction of a population in just a few generations (which, for some plants, could be less than a decade). In fact, spontaneous hybridization between crops and their wild relatives has been implicated in increased extinction risk to wild species ranging from the disappearance of wild coconuts²¹⁷ to the contamination of California’s wild walnut populations with genes from the cultivated

²⁰² Hucl, P., and M. Matus-Cádiz. 2001. *Isolation distances for minimizing out-crossing in spring wheat*. *Crop Sci.* 41: 1348-1351.

²⁰³ Longden, P. C. 1993. *Weed beet: a review*. *Aspects of Applied Biology* 35:185-194.

²⁰⁴ Ellstrand, N. C. 1988. *Pollen as a vehicle for the escape of engineered genes?* Pp. S30-S32. In, J. Hodgson and A.M. Sugden (ed.) *Planned Release of Genetically Engineered Organisms*. Elsevier, Cambridge.

²⁰⁵ Goodman, R. M., and N. Newell. 1985. *Genetic engineering of plants for herbicide resistance: status and prospects*. pp. 47-53. In, H. O. Halvorson, D. Pramer, and M. Rogul (ed.) *Engineered Organisms in the Environment: Scientific Issues*, Amer. Soc. Microbiol. Washington, D.C.

²⁰⁶ Snow, A., and P. Moran-Palma. 1997. *Commercialization of transgenic plants: Potential ecological risks*. *BioScience* 47:86-96.

²⁰⁷ Ellstrand, N. C., H. C. Prentice, and J. F. Hancock. 1999. *Gene flow and introgression from domesticated plants into their wild relatives*. *Ann. Rev. Ecol. Syst.* 30:539-563.

²⁰⁸ Boudry, P., M. Mörchen, P. Saumitou-Laprade, P. Vernet, and H. Van Dijk. 1993. *The origin and evolution of weed beets: consequences for the breeding and release of herbicide-resistant transgenic sugar beets*. *Theor. Appl. Genet.* 87: 471-478.

²⁰⁹ Mücher, T., P. Hesse, M. Pohl-Orf, N. C. Ellstrand, and D. Bartsch. 2000. *Characterization of weed beet in Germany and Italy*. *Journal of Sugar Beet Research* 3:19-38.

²¹⁰ Suneson, C. A., K. O. Rachie, and G. S. Khush. 1969. *A dynamic population of weedy rye*. *Crop Sci.* 9:121-124.

²¹¹ Sun, M., and H. Corke. 1992. *Population genetics of colonizing success of weedy rye in northern California*. *Theor. Appl. Genet.* 83:321-329.

²¹² Ellstrand, N. C., and D. R. Elam. 1993. *Population genetic consequences of small population size: implications for plant conservation*. *Ann. Rev. Ecol. Syst.* 24:217-42.

²¹³ Rhymer, J. M., and D. Simberloff. 1996. *Extinction by hybridization and introgression*. *Ann. Rev. Ecol. Syst.* 27:83-109.

²¹⁴ Huxel, G. R. 1999. *Rapid displacement of native species by invasive species: effect of hybridization*. *Biological Conservation* 89:143-152.

²¹⁵ Levin, D. A., J. Francisco-Ortega, and R. K. Jansen. 1996. *Hybridization and the extinction of rare plant species*. *Conservation Biology* 10:10-16.

²¹⁶ Wolf, D. E., N. Takebayashi, and L. H. Rieseberg. 2001. *Predicting the risk of extinction through hybridization*. *Conservation Biology* 15:1039-1053.

²¹⁷ Harries, H. C. 1995. *Coconut* (2nd ed.) . pp. 57-62. In, J. Smartt and N. W. Simmonds (ed.) *Evolution of Crop Plants*. Longman, Harlow, UK.

species.²¹⁸ If transgenes in a crop permits that crop to be grown more closely to wild relatives, because it can now better tolerate an environmental stress (e.g., increased tolerance to saline soils), the previously isolated species could interbreed, increasing the risk of extinction by hybridization for the wild population.

Risks resulting from the movement of transgenes within a crop, from one variety to another, have rarely been discussed. However, crop-to-crop hybridization may lead to the unintended natural “stacking” of transgenes, as in the case of the evolution of triple herbicide resistance in oilseed rape in Canada, producing crop volunteers that are now more difficult to control.²¹⁹ Likewise, crops transformed to produce pharmaceutical or other industrial compounds might cross-pollinate with the same species grown for human consumption with the unanticipated result of novel chemicals in the human food supply.²²⁰ While experience with traditional crops appears to offer no precedents for the latter risks, hybridization occurs so readily between crops and their wild relatives, it should occur even more easily between adjacent crops of the same species. One additional consequence of cross-pollination is the unintentional transfer of transgenes into crops that are intended to be “transgene-free.” While we recognize that this does not represent an environmental risk *per se*, the presence of transgenes in crops or crop products to be sold as “transgene-free” represent an economic hardship to the grower.

Risks Associated with Whole Plants

The transgenic plant itself may become an environmental problem if the transgenic trait(s) it expresses alters its ecological performance such that it becomes an invasive species or weed. Many crop plants pose little hazard, because traits that make them useful to humans also often reduce their ability to establish feral populations in either

agroecosystems or non-agricultural habitats. For example, lack of seed dormancy greatly reduces the ability of an annual crop to persist without human intervention. In many locations, corn is unlikely to survive for multiple generations outside of agricultural fields.²²¹

But, for some crops, weedy and/or wild populations often grow in close association with the cultivated forms of the same species in some part of their global distribution.²²² For example, sugar beets have established wild populations in the United Kingdom²²³ and, as noted above, canola establishes wild populations on French roadsides.²²⁴ Depending on location, certain crops (e.g., tomatoes) naturalize very quickly, and could become viable wild populations within a few generations. The existence of these populations demonstrates that if transgenes confer the ability to overcome factors that limit wild populations, the resultant genotype might be significantly more weedy or invasive than its nontransgenic progenitor. The fact that feral crop populations exist also reveals the difficulty of distinguishing gene flow and whole-plant hazards. Gene flow between feral crop populations and transgenic crops may create weeds that bear adaptations derived from the feral plants, such as seed dormancy that produces new invasive plants within an agroecosystem or beyond.

The factors limiting the naturalization of crop species are not well understood, and the factors can be subtle. Suppose an annual crop produces large quantities of viable seed with good seed dormancy characteristics and that the seedlings are capable of producing viable F_1 and F_2 populations. If those seeds have a germination cue such that seedlings appear at a time that makes them vulnerable to weed control or insect pests, a viable population may be precluded from establishing. Thus, the mere presence of a transgene should not be taken as *prima facie* evidence that the weediness of a crop has been altered. Many

²¹⁸ Skinner, M. W., and B. M. Pavlik. 1994. *Inventory of rare and endangered vascular plants of California*. California Native Plant Society, Sacramento, CA.

²¹⁹ Hall et al, 48:688-694.

²²⁰ Ellstrand, N. C. 2001. *When transgenes wander, should we worry?* Plant Physiol. 125:1543-1545.

²²¹ Rissler and Mellon. *The ecological risks of engineered crops*.

²²² de Wet, J. M. J. and J. R. Harlan. 1975. *Weeds and domesticates: evolution in the man-made habitat*. Econ. Bot. 29:99-107.

²²³ Longden, 35:185-194.

²²⁴ Pessel et al. 102:841-846.

crops are unlikely to become weedier by the addition of a single trait.²²⁵

However, some crops are capable of establishing wild populations in the U.S., especially those crops that are only slightly modified from their wild progenitors and which are adapted to U.S. conditions. This class includes some forage grasses, turf grasses, alfalfa, and many horticultural species. Some domesticated species are also important weeds of natural plant communities, including bird's-foot trefoil and Bermuda grass. In these crop species, the addition of a single transgene that improves some ecological characteristics could increase the weediness or invasiveness of the species, and these risks merit evaluation.

Non-target Risks

Non-target organisms are any species that are not the direct target of the transgenic crop. For example, *Bt* corn is presently targeted to control certain key pests, in particular, the European corn borer and the southwest corn borer. Any other species affected by *Bt* corn is a non-target species, and consequently, the list of potential non-target species is very long. These organisms can be grouped conveniently into five categories that are not mutually exclusive:²²⁶

1. Beneficial species, including natural enemies of pests (e.g., lacewings, ladybird beetles, parasitic wasps and microbes that cause disease), and pollinators (bees, flies, beetles, butterflies, moths, birds, and bats);
2. Non-target pests;
3. Soil organisms;
4. Species of conservation concern, including endangered species and popular, charismatic species (monarch butterfly); and
5. Biodiversity, which is the entire community of species in a given region.

Hazards can be difficult to demonstrate scientifically because experiments can rarely match field conditions, but field conditions are so variable over space and time that significant effects are hard to obtain. Changes to the natural community are

²²⁵ Keeler, K. H. 1989. *Can genetically engineered crops become weeds?* Bio/technology 7:1134-1139.

²²⁶ NRC, *Environmental Effects of Transgenic Plants*.

apt to be subtle, slow, and initially hard to measure. The following information illustrates a sample of possible risks to non-targets from transgenic plants:

Beneficial Species

In well-controlled laboratory studies, *Bt* toxin similar to that in *Bt* corn increased mortality in green lacewing larvae (a beneficial species that is a predator of many insect pests).²²⁷ Lacewing mortality significantly increased after both direct consumption of the *Bt* toxin and indirect consumption via eating caterpillars that had consumed *Bt* toxin. Field studies have been inconclusive; none of the published studies have documented an effect. Crops tolerant to broad spectrum herbicides (which are often transgenic) might cause indirect reductions of beneficial species (e.g., birds) that rely on food resources (insects and seeds) associated with the weeds killed by the herbicides to which the crops are resistant.²²⁸

Non-target Pests

Transgenic crops may have effects on non-target pests. Although we expect these effects sometimes to be positive, and sometimes to be negative, studies documenting only reductions in non-target pest populations have been published. For example, *Bt* corn protected against insects reduces the levels of some mycotoxins (fumonisin) produced by a non-target fungus in corn because *Bt* apparently also indirectly protects corn against fungus.²²⁹

Soil Organisms

No effects on soil organisms have been reported either in the limited number of laboratory or in field studies. However, *Bt* toxins leak out of corn roots into the soil and may persistently be

²²⁷ Hilbeck, A., M. S. Meier, and A. Raps. 2000. *Review on non-target organisms and Bt plants*, EcoStrat GmbH, Zurich, Switzerland.

²²⁸ Watkinson, A. R., R. P. Freckleton, R. A. Robinson, W. J. Sutherland. 2000. *Predictions of biodiversity response to genetically modified herbicide-tolerant crops*. Science 289: 1554-1557.

²²⁹ Munkvold, G. P., R. L. Hellmich, L. Richard, and L. G. 1999. *Comparison of fumonisin concentrations in kernels of transgenic Bt maize hybrids and nontransgenic hybrids*. Plant Disease 83:130-138.

adsorbed to soil particles for more than nine months.²³⁰ The consequences of this recently discovered persistence have not yet received much research attention or discussion. However, some effects are likely. For example, a number of *Bt* toxins have been found to be toxic to bacteria eating soil nematodes.²³¹

Species of Conservation Concern

Reports of the toxic effects of *Bt* corn pollen eaten by monarch butterfly larvae²³² captured widespread attention, in part because the species is so well known. The scientific data in this issue are still emerging, but it appears that the effects of *Bt* pollen on monarch mortality are highly variable, depending on a variety of factors, such as the density of *Bt* corn pollen and the *Bt* genotype creating that pollen.²³³ The issue received comprehensive research attention in a series of papers published in the 9 October 2001 issue of the Proceedings of the National Academy of Sciences, USA. The consensus of these papers is that the effects of *Bt* on monarch larvae are indeed idiosyncratic, varying with both maize genotype and environmental conditions.

Biodiversity is elusive because it embraces many variables, including the number of species, their relative abundance, the way they interact, and whether they are indigenous or exotic. From a conservation perspective, preservation of native species is a priority. Relatively little is known about the potential effects of transgenic crops on biodiversity from this perspective. However, as discussed above, the use of herbicide-tolerant crops might end up reducing biodiversity by locally eliminating wild plant species that serve

as food sources for insects, and microorganisms. Such a reduction in biodiversity might then reduce the population densities of birds that rely on this biodiversity for food. Although this topic has been discussed specifically for transgenic herbicide tolerant crops,²³⁴ it is, in fact, a potential impact of all herbicide tolerant crops, regardless of their origin.

The state of knowledge about non-target effects of transgenic plants is improving slowly, but controversy surrounds each published study. The biggest gap in this research is establishing scientifically rigorous assessment protocols that take into account the unusual exposure routes of transgene products. Consequently, considerable scientific work remains before evaluation of non-target effects is standardized.

Risks Associated with Herbicide Use

Herbicides are chemicals used to kill plants. In several crops, weeds are closely related to those crops, preventing the use of herbicides to control them, because such herbicides would usually also harm the crops. The harmful effects of herbicides on crops are circumvented when herbicide-tolerant crops are created so that they are unaffected by a specific herbicide. Such crops are often transgenic, but some are created through traditional plant improvement methods.²³⁵ As opposed to pest-resistant crops, transgenic herbicide-resistant crops are expected to result in the increased use of certain pesticides in the environment and possible decrease of others. Comparison of herbicide use on transgenic soybean in 1998 revealed that, on average, more herbicides were applied in that year but in fewer applications. The increase was primarily due to a 7.3 times increase in pounds of glyphosate used per acre with smaller increases in seven other herbicides; use of 16 other herbicides declined.²³⁶ The mix of herbicide being used on soybean has changed – the use of glyphosate increased from 20% in 1995 to 62% in 1999, and the use of the most widely used herbicide, Imazethapyr,

²³⁰ Tapp, H, and G. Stotzky. 1998. Persistence of the insecticidal toxin from *Bacillus thuringiensis* subsp. *kurstaki* in soil. *Soil Biol. Biochem.* 30: 471-476.

²³¹ Borgonie, G., M. Claeys, F. Leyns, G. Arnaut, and D. de Waele et al. 1996. *Effect of a nematocidal Bacillus thuringiensis strain on free-living nematodes*. 3. Characterization of the intoxication process. *Fund. Appl. Nematol.* 19:523-528.

²³² Losey, J. E., L. S. Rayor, and M. E. Carter. 1999. *Transgenic pollen harms monarch larvae*. *Nature* 399:214

²³³ Wraight, C. L., A. R. Zangerl, M. J. Carroll, and M. R. Berenbaum. 2000. *Absence of toxicity of Bacillus thuringiensis pollen to black swallowtails under field conditions*. *Proc. Natl. Acad. Sci. (USA)* 97:7700-7703.

²³⁴ Watkinson et al. 289:1554-1557.

²³⁵ Harrison, H. F. 1992. *Developing herbicide-tolerant crop cultivars: introduction*. *Weed Technol.* 6:613-614.

²³⁶ Wolfenbarger and Phifer. 290:2088-2093.

decreased from 44% to 16% during the same time period. In addition, the number of herbicide applications reduced 12% during the same time period. These changes in herbicide use occurred even though the total number of soybean acres increased by 18% between 1995 and 1999. The decrease in herbicide applications demonstrates growers are using fewer active ingredients and making fewer trips over the field, which translates into ease of management.

Some believe that the changes in herbicide use may be good for the environment because glyphosate is less toxic and less likely to persist in the environment than the herbicides it has replaced.²³⁷ Unlike the case of soybean, increased acreage of herbicide-tolerant cotton or corn did not result in a reduction in the amount of herbicide used on these two crops.²³⁸ In at least one case, the herbicide associated with a commercially released transgenic herbicide tolerant plant (bromoxynil tolerant cotton) is classified by EPA²³⁹ as a possible carcinogen. Although it is clear that herbicide use patterns have changed with increased use of transgenics, it is not clear whether those changes are, as a whole, beneficial or detrimental.

Risks Associated with Resistance Evolution

As with conventionally bred crops, resistance evolution can occur in pests that are targeted for control by or are associated with the transgenic crop. The evolution of resistant pests is a potential environmental hazard because alternative, more environmentally damaging controls may be needed for continued control. In an emergency, new control tactics may be rushed into use before their environmental

risks are completely assessed. Insects, weeds, and microbial pathogens have all occasionally evolved resistance to control tactics used against them.^{240, 241, 242} Insect resistance to *Bt* crops is considered inevitable,²⁴³ and efforts are being made by some growers to manage resistance evolution to these transgenic crops. For example, the Environmental Protection Agency guidelines^{244, 245} on the cultivation of transgenic crops mandates farmers to plant refuges of non-*Bt* crops as border rows along with *Bt* crops to prevent/decrease the rate of resistant evolution. Despite such efforts to prevent *Bt* resistance evolution among insect pests, organic farmers are still concerned about the economic consequences to their industry if and when such pest-resistance evolves because of widespread use of *Bt* crops. Such concerns are not without merit, as pest-resistance has already emerged on a very large scale in modern agriculture.²⁴⁶ Therefore, organic farmers concerns should be given serious consideration by all parties involved in transgenic crop industry as *Bt* sprays are extensively and effectively employed by organic farmers to control insect pests of their crop plants. Virus resistant transgenic crops have not been used extensively, but many viruses have evolved new virulence and become capable of infecting conventionally

²³⁷ Heimlich, R. E., J. Fernandez-Cornejo, W. McBride, C. Klotz-Ingram, S. Jans, and N. Brooks. 2000. *Adoption of genetically engineered seed in U.S. agriculture: Implications for pesticide use*. USDA (ERS). Unpublished paper presented at the 6th International Symposium on the Biosafety of Genetically Modified Organisms, Saskatoon, Canada, 8-13 July 2000.

²³⁸ USDA (ERS). *Genetically engineered crops for pest management*.

²³⁹ EPA (Environmental Protection Agency). 1997. Office of Prevention, Pesticides and Toxic Substances memorandum. April 8, 1997, Extension of conditional registration for the use of bromoxynil on transgenic cotton. pp. 4-6.

²⁴⁰ Barrett, S. C. H. 1983. *Crop mimicry in weeds*. *Economic Botany* 37:255-282.

²⁴¹ Georghiou, G. P. 1986. *The magnitude of the resistance problem*. pp.14-43. In, *Pesticide Resistance: Strategies and Tactics for Management* (ed.) National Research Council. Washington, D.C. National Academy Press, Washington, D.C.

²⁴² Green, M. B., H. M. LeBaron, and W. K. Moberg (ed.). 1990. *Managing Resistance to Agrochemicals: From Fundamental Research to Practical Strategies*. Amer. Chem. Soc. Symp. Series No. 421.

²⁴³ Liu, Y. B., B. E. Tabashnik, T. J. Dennehy, A. L. Patin, A. C. Bartlett. 1999. Development time and resistance to *Bt* crops. *Nature* 400:519.

²⁴⁴ EPA (Environmental Protection Agency). 1999. EPA and USDA Position paper on insect resistance management on *Bt* crops. (www.epa.gov/pesticides/biopesticides/otherdocs/bt_position_paper_618.htm).

²⁴⁵ USDA (NASS). 1999. www.usda.gov/nass/pubs.

²⁴⁶ Georghiou, pp.14-43.

bred virus-resistant crops.²⁴⁷ Fungal and bacterial resistance is not yet commercially available in transgenic crops, but both groups of organisms have evolved resistance to conventional crop resistance, often within five years.

Evolution of herbicide-tolerant weeds is an indirect environmental risk. Herbicide-tolerant transgenic crops are designed so that specific herbicides can be used to control weeds, usually after the crop has emerged. In theory, these post-emergence weed controls might allow herbicides to be used only as needed, reducing herbicide applications to crops (see previous paragraphs). In some crops, these post-emergence herbicides might replace herbicides that are more damaging to the environment. As weeds evolve resistance to these herbicides, the potential environmental benefits could be lost. Such is the case with the evolution of multiple herbicide-resistant canola plants²⁴⁸ for which 2,4-D, a carcinogenic herbicide, is recommended to kill the newly evolved weeds.

TRANSGENIC CROPS AND CALIFORNIA

Currently, 53 different transgenic crop varieties have been deregulated for commercial planting in the U.S. Only a fraction of these are currently grown in California. Some (like the Flavr Savr-TM tomato) have been withdrawn from the market, some (like virus-resistant papaya) cannot be grown in California, and some (herbicide-resistant sugar beet) are not grown because industrial processors are reluctant to accept produce from transgenic plants. The largest portion of California's current transgenic agricultural acreage is planted in *Bt* cotton. But that is a small fraction of America's total transgenic acreage, which is concentrated in those states that grow corn and soybeans.

Will the benefits and risks realized in the nation's acreage serve as a model for the future impacts of transgenic plants in California?

To date, about 900 applications for California field tests of transgenic plants have been filed with USDA-APHIS, the federal agency that regulates such tests. How these potential transgenic crops impact California's environment relative to the foregoing discussion depends on how different California is compared to rest of the nation in terms of its crops and environment.

California is rich in natural resources and has a great deal of physical, biological, and climatic diversity. California is home to "...highest peaks and the lowest valleys ..., 11 biogeographic regions, 396 habitat types...[and it] is home to more plant and animal species than any other state."²⁴⁹ Unfortunately, nearly 50% of its plant taxa are considered endangered due to human activity including habitat degradation, land conversion, fragmentation, and alien species introduction.²⁵⁰ Not surprisingly, California works to save these resources, leading the nation in environmental protection legislation.

California is also legendary for its agricultural industry. The combination of available water, fertile soil, and a Mediterranean climate provides nearly ideal growing conditions for a tremendous variety of crop plants. Moderate year-round temperatures in most of the state allow year-round crop production, while diverse microclimates provide local niches for unique specialty crops. California is home to the largest food and agriculture economy in the U.S. Of California's \$27 billion total farm income, \$18 billion comes from plants – a diverse array of fruits, vegetables, field crops, and nursery plants, totaling around 350 different crop plants in California.²⁵¹

²⁴⁷ Fraser, R. S. S. 1989. *The genetics of plant-virus interactions mechanisms controlling host range resistance and virulence*. In, R. S. S. FRASER (ed.) Recognition and Response in Plant-Virus Interactions. Workshop, NATO ASI (Advanced Science Institute) Series, Series H Cell Biology, VOL. 41, Chichester, England, UK, April 12-16, 1989. Springer-Verlag, Berlin, Germany.

²⁴⁸ Hall, L.; K. Topinka, J. Huffman, L. Davis, and A. Good. 2000. *Pollen flow between herbicide-resistant Brassica napus is the cause of multiple-resistant B. napus volunteers*. Weed Sci. 2000. 48:688-694.

²⁴⁹ Hickman, J. C. (ed.) 1993. *The Jepson Manual: Higher Plants of California*. University of California Press, Berkeley, California.

²⁵⁰ Hickman, *The Jepson Manual: Higher Plants of California*.

²⁵¹ CDFA (California Department of Food and Agriculture Resource Directory). 2000. *Agriculture Statistical Review*. (<http://www.cdfa.ca.gov/docs/CAStats.pdf>)

California is also a national leader in the nation in organic agriculture. Compared to high yielding, resource intensive agriculture, organic agriculture is often considered by some to be more sustainable and to foster human and environmental health.²⁵² Currently there are more than 2,000 organic producers in California, who sold \$156 million worth of produce in 1998. Furthermore, the industry has been growing in popularity with consumers as sales have been increasing at the rate of 20-24% every year for the last 10 years. More than 70 commodities representing every major crop are produced and marketed as organic, among them vegetables, fruits, and nuts dominate.²⁵³

We compared the leading 20 crops grown both in the U.S. and in California (Table 2). Eleven crops appear on both lists. Similarly, both the lists contain five crops for which one or more deregulated transgenic cultivars exist. For these shared transgenic cultivars, the potential risks and benefits for California's environment may not be much different from what has been already discussed in this chapter for the nation.

However, despite their similarities, the list of 20 leading crops grown in the U.S. and California (Table 2) also shows substantial difference in the types of crops grown on these two scales. Cereal and oilseed crops make up most of the 20 leading crops at the national level, whereas most of the top 20 leading crops in California are fruits and vegetables. For example, California accounts for more than 80% of grapes and tomatoes grown in the U.S. (Table 2), and for crops such as almonds, artichokes, olives, and walnuts California is essentially the sole producer (99% or more) in the nation.²⁵⁴ Any transgenic crops created for these four crops could, therefore, affect California's environment, either positively or negatively, more than any other state in the U.S. And, indeed, many of California's specialties are on the aforementioned list of field trials.

Moreover, fruits, vegetables, and nuts dominate California's organic agriculture, and some organic growers are asking for stricter guidelines for transgenic crops in California. California's distinction in types and variety of its crops and diversity of its agricultural practices may demand a different approach for dealing with the risks and benefits of how transgenic crops impact the environment.

DISCUSSION

The available evidence suggests that transgenic crops may hold both promise and threat for the environment depending upon a variety of specific factors including the type of transgenic crops under cultivation, the nature of transgenic traits involved, and the geographic location of crops in relation to wild relatives. For example, a transgene for pest resistance may carry more risk in terms of harm to non-target insects than a transgene that improves nutritional quality of a seed. Accordingly, the risk-benefit analysis of how transgenic crops impact the environment needs to consider these factors in the analysis in addition to a baseline comparison with traditional practices (that range from large industrial farms to small organic growers and the great variety of practices between these extremes). Although we have a fairly good knowledge of what factors should go into a qualitative risk-benefit analysis while dealing with impacts of transgenic crops on the environment, quantifying the specifics will be elusive. Problems remain as to how to predict the likelihood of some long-term risks associated with transgenes to the environment. Also, long-term risks associated with transgene escape into wild relatives are almost impossible to predict from short-term risk analysis.²⁵⁵ Many benefits are also difficult to quantify, such as benefits of reduced pesticide use by pest-resistant transgenic crops on the non-target insects. Despite these limitations, identifying the potential risks and benefits of how transgenes impact the environment as accurately as possible is the most important step in risk-benefit analysis. Any improper addition or deletion of risks or benefits to the analysis may

²⁵² NRC, *Committee on the Role of Alternative Farming Methods in Modern Production Agriculture*.

²⁵³ CDFA, <http://www.cdfa.ca.gov/docs/CAStats.pdf>

²⁵⁴ CDFA, <http://www.cdfa.ca.gov/docs/CAStats.pdf>

²⁵⁵ Winrock International. *Transgenic crops: An environmental assessment*.

seriously undermine the usefulness of the risk-benefit analysis.

Some of the expected benefits from transgenic crops have been realized, as in case of transgenic insect-resistant cotton. Overall, an increase in transgenic cotton cultivation has substantially reduced the amount of pesticide use. Nonetheless, certain potential benefits of cultivating transgenic crops on the environment have not yet been realized. For example, increased use of high-yielding transgenic crops is expected to reduce the area under cultivation, and subsequently a fraction of this unused land area is expected to be returned for wildland development. As yet, there are no data to confirm or refute this benefit, although the record for high-yield agriculture clearly indicates that vast areas of land not farmed resulted from advances in technology. Finally, some benefits are simple to visualize, but difficult to quantify, as in case of benefit accrued to non-target organisms due to reduced pesticide use by growing pest-resistant crops.

Detection of slow and cumulative negative impacts of transgenic crops on the environment is harder to measure relative to immediate benefits. For example, it is difficult to monitor the early and rare events associated with an escaped transgene from a crop into wild population and, therefore, difficult to measure the affects of that transgene in the wild.²⁵⁶ Nonetheless, certain predicted environmental risks of transgenic crops to the environment have already been documented; for example, the evolution of multiple herbicide-resistance in feral canola²⁵⁷ discussed above.

California shares some of the transgenic crops that are being cultivated across the nation and will benefit from the data collected on such crops here and elsewhere in the U.S. However, California will be the sole U.S. state testing transgenic crops on fruits, vegetables, and nuts (California's specialties). For some of these crops, transgenic cultivars are already being developed and may require additional

consideration to assess their risks and benefits to California's diverse environment.

The evolution of transgenic crops will change the landscape of agriculture in the 21st century. A new generation of crops will appear soon. There are transgenic crops to be grown as chemical factories producing pharmaceuticals and other industrial compounds.²⁵⁸ As a consequence, the benefits and risks of these crops have hardly been examined. Therefore, there is an urgent need to invest more labor and capital in transgenic risk-benefit research to safely and effectively utilize the true benefits of transgenic crops. A systematic national monitoring of transgenic crop plants including follow up studies on risk-benefit analysis may be beneficial both for the transgenic crop industry and for the consumers.²⁵⁹ Presently, the impacts of these crops are receiving occasional research attention from land-grant universities.²⁶⁰ These might well be the best venues for conducting focused, long-term risk-benefit research on and analysis of transgenic plants.

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²⁵⁶ Kareiva, P., I. M. Parker, and M. Pascual. 1996. Can we use experiments and models in predicting the invasiveness of genetically engineered organisms? *Ecology* 77:1670-1675.

²⁵⁷ Hall et al. 48:688-694.

²⁵⁸ Dunwell, J. M. 1999. Transgenic crops: The next generation, or an example of 2020 vision. *Ann. Bot.* 84: 269-277.

²⁵⁹ NRC, *Environmental Effects of Transgenic Plants*.

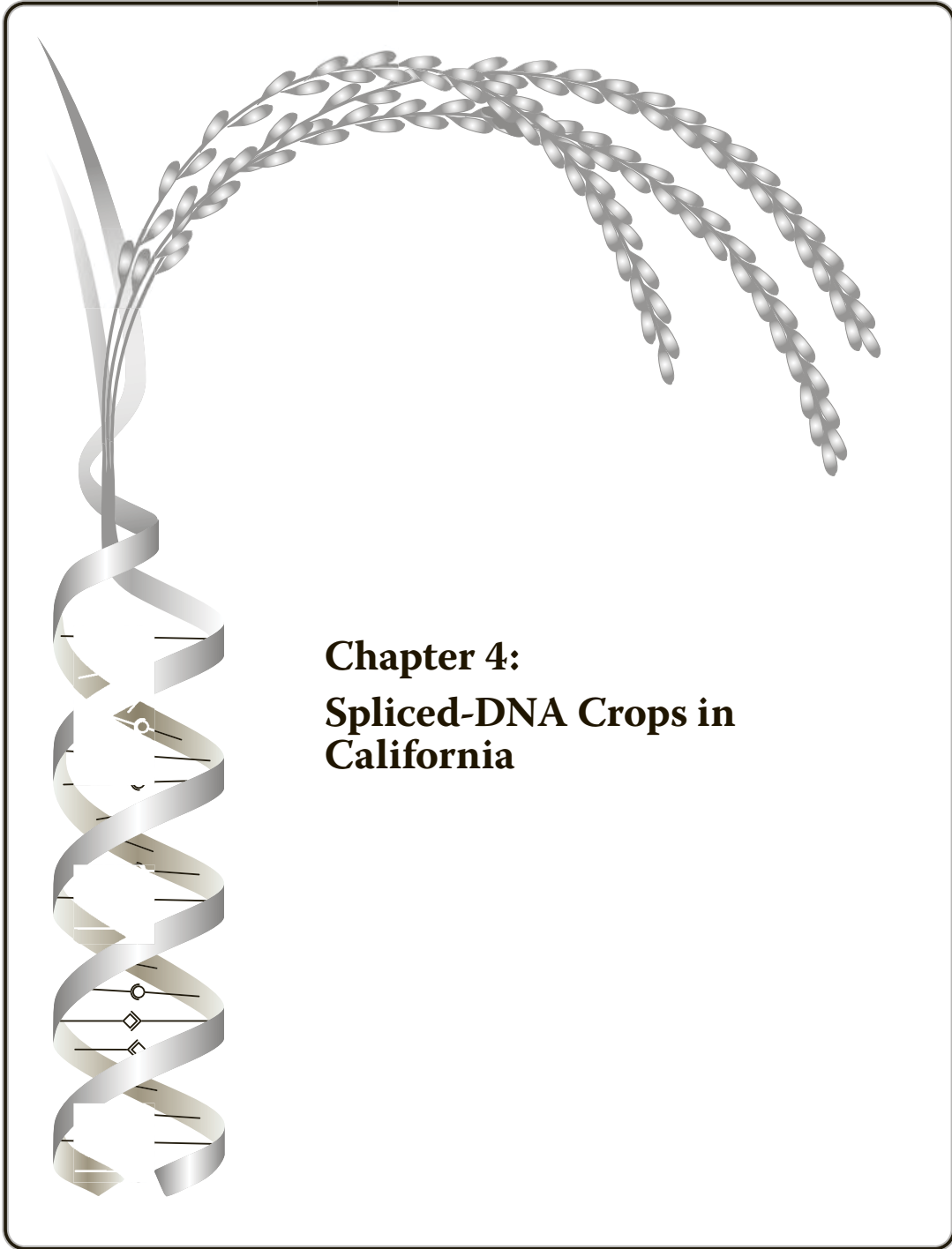
²⁶⁰ Pretty, J. 2001. *The rapid emergence of genetic modification in world agriculture: contested risks and benefits*. *Environmental Conservation*. 28:248-262.

Rank	Crops in California ^a	Area planted (106 hectares)	Rank	Crops in the U.S. ^b	Area planted (106 hectares)
1	Alfalfa	0.38	1	Maize (including sweet corn)	32.5
2	Cotton lint, all	0.34	2	Soybean	30.1
3	Grapes, all	0.32	3	Wheat	25.3
4	Rice	0.20	4	Alfalfa	9.3
5	Almond (shelled)	0.19	5	Cotton	6.3
6	Wheat, all	0.18	6	Sorghum	4.3
7	Tomato, all	0.15	7	Barley	2.4
8	Lettuce, all	0.09	8	Oats	1.8
9	Maize, grain	0.082	9	Rice	1.2
10	Oranges, all	0.081	10	Sunflower	1.1
11	Walnuts	0.077	11	Beans, dry and snap	0.8
12	Beans, dry	0.053	12	Rapeseed (including canola)	0.6
13	Barley	0.05	13	Beets, sugar and table	0.6
14	Broccoli	0.05	14	Groundnuts (peanuts)	0.5
15	Sugar beets	0.043	15	Potatoes	0.5
16	Carrots	0.037	16	Rye	0.5
17	Prunes, dry	0.034	17	Sugar cane	0.4
18	Pistachios	0.029	18	Grapes	0.4
19	Sunflower		19	Oranges	0.3
20	Canola		20	Flaxseed	0.2

^a Estimated area of production in California for 2000 (California Department of Food and Agriculture Resource Directory)

^b Estimated area of production in U.S. for 2000 (USDA)

Table 2. The top 20 crops grown in California and the United States, and the transgenic crops no longer regulated by USDA (in boldface)



**Chapter 4:
Spliced-DNA Crops in
California**

Chapter 4: Spliced-DNA Crops in California

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INTRODUCTION

A revolution in crop agriculture resulted, since 1996, in substantial penetration of spliced-DNA cultivars into U.S. plantings of cotton, soybean and corn. California generally has been a leader in agricultural innovation, but only cotton, among spliced-DNA crops, has seen significant production in California. Although transgenic cotton came to California later than it was adopted elsewhere in the U.S., transgenic cotton accounted for 36% of California's cotton acreage in 2001. Spliced-DNA corn and squash lines also have been planted commercially in California, but on more limited acreage than for spliced-DNA cotton. About 30 crop species have been the subjects of permit requests for transgenic field-testing in California, suggesting continued optimism on the part of seed companies and other organizations about the future of spliced-DNA crops in California.

Although California has not seen extensive planting of spliced-DNA crops other than cotton, Calgene, Inc., of Davis, California, produced the first spliced-DNA crop to reach the market. Circumstantial evidence available in the 1980s suggested that the tomato fruit enzyme polygalacturonase (PG), because of its ability to dissolve cell-wall pectin, was key to fruit softening. Calgene researchers introduced a reverse-orientation ("antisense") version of a cloned PG gene with the intent of preventing or greatly reducing PG accumulation and thereby delaying fruit softening. The objective was to avoid the practice of picking and transporting green fruit that subsequently would be reddened, but not ripened, by treatment with the plant growth substance ethylene. The PG antisense technology was expected to produce vine-ripened, and therefore flavorful, tomato fruit that was firm enough to be transported to fresh fruit markets as ripe fruit. Some of Calgene's antisense transformed tomato lines generated as little as 1% of the PG found in conventional tomato fruit.

In October 1992, the U.S. Department of Agriculture found that the PG-antisense tomato lines were not a "plant-pest" risk and would not require permits for field-testing or transport. Data submitted by Calgene to the U.S. Food and Drug Administration (FDA) included animal feeding studies and extensive chemical analyses. The results showed the PG-antisense tomato to be indistinguishable in almost every way from traditional tomatoes.²⁶¹ The exceptions were that fruit cell-wall pectin degraded more slowly, and tomato paste had a higher viscosity, both expected consequences of reduced PG in the fruit. In 1994, the FDA concluded that the antisense gene construction and the kanamycin resistance gene construction used as an adjunct in transforming plants, and the products of the introduced genes, were approved for commercial production and sale.²⁶²

On May 21, 1994, the genetically engineered Flavr Savr tomato was introduced in Davis and in Chicago. Demand for this product was high and remained high, but the product was never profitable because of high production and distribution costs. The PG antisense tomato was withdrawn from production.²⁶³ However, in 1996, Zeneca, under license, introduced into the United Kingdom, paste from PG-antisense tomatoes grown and processed in California. The Sainsbury and Safeway chains sold more than 1.8 million cans, clearly labeled as derived from genetically engineered tomatoes, from 1996 through early

²⁶¹ Redenbaugh K, Hiatt W, Martineau B, et al. 1992. Safety Assessment of Genetically Engineered Fruits and Vegetables: A Case Study of the Flavr Savr™ Tomato. Boca Raton, Fla.: CRC Press. 267 pp.

²⁶² Martineau B. 1997. From lab bench to marketplace: The Calgene Flavr Savr™ tomato. Chapter 2. In: PM Gresshoff (ed.). Technology Transfer of Plant Biotechnology. Boca Raton, Fla.: CRC Press. p 13-23.

²⁶³ Martineau, B. (2001). First Fruit, pp. 270. New York: McGraw-Hill.

1999. Reduced processing costs, attributable to the PG antisense gene, allowed a 20% lower price. The paste from genetically engineered tomatoes initially out-sold conventional tomato paste at many locations. However, sales declined after a British Broadcasting Company program in August of 1998 presented conclusions purportedly showing adverse effects in spliced-DNA potatoes that were attributed to the transgene process. The conclusions stated in the broadcast were later found to be incorrect by independent analyses.^{264, 265} However, Safeway and Sainsbury declared that their house brands would not have genetically engineered ingredients. The Zeneca product did not return to grocery store shelves, with a corresponding loss to California agriculture.²⁶⁶

What are the barriers to development and adoption of spliced-DNA crops in California? California's crop agriculture is diverse. By comparison with cotton, soybean, and corn crops, California's crop economy consists mainly of "minor" crops. The high costs of research, and of satisfying regulatory requirements, dictated that very-high-acreage crops received first attention for development of spliced-DNA lines. The research costs of creating new spliced-DNA crops have declined as new and improved gene constructions and recipes for plant transformation and regeneration have been developed. However, costs associated with regulations and use of intellectual property probably have remained high.

Future public acceptance of the products of spliced-DNA crops remains uncertain in spite of six years of extensive planting. In that time, there has been no documented adverse effect to food safety or to the environment and no validated scientific evidence for developing problems that would be different from those associated with conventionally

bred crops. Nevertheless, the actions of a minute minority of the public, the vandals who on occasion have destroyed crops and facilities they believe have connections to spliced-DNA work, increase the costs and decrease the investments in spliced-DNA crop technology. They also make this report less complete than it might otherwise be, because of reluctance by those concerned with the safety of their facilities and personnel to release information about current research, field tests, and commercial plantings of spliced-DNA crops.

COTTON

Cotton was cultivated in the coastal valleys of California under the direction of the Spanish Franciscan monks in the first half of the 19th century. After California statehood and through about 1890 a variety of experimental and commercial plots were planted, but production was greatly limited by sources of reliable water and labor, and little or no cotton production was continuous at any location from the 19th into the 20th century. However, in the 20th century, cotton became at times the largest cash crop of California,²⁶⁷ and it remains very important for both domestic consumption and export. The economic value of cotton lies primarily in the fiber, the lint, and cotton accounts for about half of all of the fiber used in the world's textile industry. However, cotton also is a food crop. Some cotton seed is crushed for the production of cooking oil and other food products. The by-products of crushing, as well as whole cotton seed, are consumed by cattle, primarily dairy cattle in California.^{268, 269}

Almost all of the world's cotton production is derived from two crop species, *Gossypium hirsutum*, commonly referred to as "Upland cotton" and *Gossypium barbadense*. Among *G. barbadense* cultivars, which in general have long fibers, are

²⁶⁴ Ewen SWB, Pusztai A. 1999. Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* (N. Am. Ed.) 354:1353-4.

²⁶⁵ U.K. House of Commons. 1999. Select Committee on Science and Technology, Session Report, genetically modified foods. HC286, Vol. 1, ISBN 0102314993, <http://www.fern.org/pmhp/dc/genetics/sci-tec.htm>.

²⁶⁶ Bruening, G. and Lyons, J.M. (2000) The case of the FLAVR SAVR tomato. *California Agriculture* 54(4), 6-7.

²⁶⁷ Musoke, M.S. and A.L. Olmstead, *A History of Cotton in California: a Comparative Perspective*. 1980, Agricultural History Center, University of California, Davis: Davis, CA. p. 42 plus tables and references.

²⁶⁸ Williams, E.P., *Cotton Industry Perspective*. 2000, Biotechnology Roundtable: Sacramento, CA. p. 5.

²⁶⁹ CCGA, *Cotton Facts*. http://www.ccgga.org/cotton_information/calif_cotton.html. 2002, California Cotton Ginners and Growers Association: Fresno, CA.

the extra-long staple (ELS) Pima cottons. Both worldwide and in the U.S., about 95% of cotton production is derived from *G. hirsutum* Upland cottons. In contrast to wild diploid cotton species, both cultivated species are tetraploids of ancient origin.^{270, 271} *G. hirsutum* is native to Central America and Mexico and *G. barbadense* is native to South America.²⁷² Archeological evidence shows *G. hirsutum* cultivation 5,500 years ago in present day Mexico and *G. barbadense* in Peru 4,500 years ago.^{273, 274}

Cotton justly can be characterized as a “natural fiber” in the sense that it is of biological origin rather than the result of chemical synthesis. As is the case for virtually all other crops,²⁷⁵ however, cotton cultivars have been subject to intense genetic manipulation. The elite cultivars of cotton planted in California are so diverged from cottons that have not been subject to selection by humans that “natural” in a genetic sense is not an accurate adjective.

Genetic Improvement of Upland Cotton

Cotton is among the most intensely bred crops, by both old and new technologies. *G. hirsutum* seed was imported into the U.S. from the West Indies and Central America in the 18th century and became widely planted in the interior of the U.S. South, where lines that are day-length

neutral for flowering were selected before the early 19th century.^{276, 277} Accidental and purposeful crossing between the newly introduced lines from Mexico and elsewhere and previously introduced lines resulted in hybrids with such favorable new traits as greater disease resistance, early ripening, improved picking, and longer staple. By 1860, the total cash value of cotton was greater than that of all other U.S. crops combined, and cotton exports exceeded the value of U.S. manufactured goods exports by a factor of five.²⁷⁸

Later in the 19th century, hybridization and selection programs produced many well-defined commercial cotton varieties (cultivars).²⁷⁹ The English translation of Mendel’s *Experiments in Plant Hybridization* appeared in 1901, and the first mention of Mendel’s theory in the context of cotton appeared in 1907.²⁸⁰ The cotton gene pool has been enriched in the 20th century by applications of Mendel’s principles and by seed collection trips to southern Mexico, Guatemala, and elsewhere. Cotton researchers were among those who pioneered research practices such as replication of treatments in field plots and the application of statistical methods in genetical and physiological research,²⁸¹ as well as applications of quantitative genetics.²⁸²

Table 3 demonstrates the improvement in Upland cotton quality characters that have been achieved primarily by traditional breeding. However, cotton also has been improved, intentionally and not, by

²⁷⁰ Reinisch, A.J., et al., A detailed RFLP map of cotton, *Gossypium hirsutum* X *Gossypium barbadense*: Chromosome organization and evolution in a disomic polyploid genome. *Genetics*, 1994. 138(3): p. 829-847.

²⁷¹ Zhao, X., et al., *Macromolecular organization and genetic mapping of a rapidly evolving chromosome-specific tandem repeat family (B77) in cotton (Gossypium)*. *Plant Molecular Biology*, 1998. 38(6): p. 1031-1042.

²⁷² Munro, J.M., *Chapter 3. Taxonomy*, in *Cotton*. 1987, Longman Scientific and Technical and John Wiley & Sons: New York. p. 27-40.

²⁷³ Turner, J., *Chapter 1. Introduction*, in *White Gold Comes to California*. 1981, California Planting Cotton Seed Distributors: Bakersfield, California. p. 252.

²⁷⁴ Hancock, J.F., *Chapter 11. Fruits, vegetables, oils and fibers*, in *Plant Evolution and the Origin of Crop Species*. 1992, Prentice Hall: Englewood Cliffs, New Jersey. p. 260-288.

²⁷⁵ van Alfen, N.K., *How natural is modern agriculture?* *California Agriculture*, 2000. 54(4)(4): p. 47-48.

²⁷⁶ Tracy, S.M., *Cultivated varieties of cotton*, in *Bulletin No. 33. The Cotton Plant*, A.C. True, Editor. 1896, U.S. Department of Agriculture Office of Experiment Stations: Washington, D. C. p. 197-224.

²⁷⁷ Munro, Chapter 3, 1987.

²⁷⁸ Turner, 1981.

²⁷⁹ Tracy, 1896.

²⁸⁰ Munro, J.M., *Chapter 1. The origin of cotton*, in *Cotton*. 1987, Longman Scientific and Technical and John Wiley & Sons: New York. p. 6-26.

²⁸¹ Munro, Chapter 1, 1987.

²⁸² McCarty, J.C. and R.G. Percy, *Chapter 4. Genes from exotic germplasm and their use in cultivar improvement in Gossypium hirsutum L. and G. barbadense L.*, in *Genetic Improvement of Cotton. Emerging Technologies*, J.N. Jenkins and S. Saha, Editors. 2001, Science Publishers, Inc.: Enfield, New Hampshire. p. 344.

other techniques and phenomena that alter, locally or on a broader scale, the nucleotide sequences in cotton DNA. Tissue culture, or sometimes the use of plant growth regulatory substances on the intact plant, provides the ability to “rescue” a cotton ovule or embryo that would not proceed to seed formation without intervention.²⁸³ As examples of inter-species (interspecific), wide genetic crosses of cotton, *G. hirsutum* has been crossed to *G. tomentosum* to introduce resistance against boll rot and to *G. raimondii* to introduce resistance against a rust fungus.²⁸⁴ *G. hirsutum* also was crossed to *G. sturtianum* to reduce seed content of the toxic sesquiterpenoid gossypol.²⁸⁵ Genetic wide crosses and the actions of endogenous transposons and retrotransposons, which are well represented in cotton,²⁸⁶ have created new, broad scale juxtapositions of DNA sequences.²⁸⁷

Cotton cultivars, particularly some grown in Pakistan and China, have significant improvements in yield and in the architecture of the plant that resulted from induced mutations.^{288, 289} Protoplasts are readily generated from cotton tissue, and cotton plants have been regenerated from

protoplasts with difficulty.^{290, 291} Some hybrids from protoplast fusion may be fertile and therefore potentially useful in breeding. Plants regenerated from protoplasts exhibit an enhanced degree of variation, some of which is maintained in subsequent generations and may be regarded as genetic “somaclonal variation”.²⁹² Although somaclonal variation may not have contributed significantly to cotton improvement, the technology is illustrative of the extensive manipulation of the plant genome that underlies modern cultivars.

Spliced-DNA Upland Cotton in the U.S.

The technology for controlled plant genetic transformation was invented in the mid-1980s by combining plant regeneration capabilities, the ability to manipulate and amplify DNA sequences in the bacterium *Escherichia coli*, and the plant-transforming action of non-plant pathogenic lines of the bacterium *Agrobacterium tumefaciens*. “Spliced-DNA” fertile plant lines can be created by introducing new DNA from any biological source, or even chemically synthesized DNA. The result can be cultivars with new Mendelian genes. The first commercial transgenic cotton followed shortly after the Flavr Savr™ tomato, which was the first spliced-DNA crop of any kind to be commercialized. “BXN cotton,” which currently is planted in California, was introduced in 1995. BXN cotton is tolerant of the herbicide bromoxynil because of an introduced gene of bacterial origin that degrades the herbicide to non-toxic products. “*Bt* cotton,” resistant against certain Lepidopteran worms, the tobacco budworm, the cotton bollworm, and the pink bollworm, was introduced in 1996. The *Bt* gene also is of bacterial origin. The *Bt* insecticidal protein is part of the delta endotoxin derived from *Bacillus thuringiensis*. “RR cotton” (“Roundup Ready™” i.e., cotton tolerant to the herbicide glyphosate) was introduced in 1997.

²⁸³ Altman, D.W., Exogenous hormone applications at pollination for in vitro and in vivo production of cotton interspecific hybrids. *Plant Cell Reports*, 1988. 7(4): p. 257-261.

²⁸⁴ Goodman, R.M., et al., Gene Transfer in Crop Improvement. *Science* (Washington D C), 1987. 236(4797): p. 48-54.

²⁸⁵ Altman, D.W., D.M. Stelly, and R.J. Kohel, Introgression of the glanded-plant and glandless-seed trait from *Gossypium sturtianum* Willis into cultivated Upland cotton using ovule culture. *Crop Science*, 1987. 27(5): p. 880-884.

²⁸⁶ Baker, R.J., J.L. Longmire, and R.A. Van Den Bussche, Organization of repetitive elements in the Upland cotton genome (*Gossypium hirsutum*). *Journal of Heredity*, 1995. 86(3): p. 178-185.

²⁸⁷ Hancock, J.F., Chapter 1. Mutation and genetic variability, in *Plant Evolution and the Origin of Crop Species*. 1992, Prentice Hall: Englewood Cliffs, New Jersey. p. 3-32.

²⁸⁸ Jain, S.M., D.S. Brar, and B.S. Ahloowalia, *Somaclonal Variation and Induced Mutations in Crop Improvement*. 1998, Dordrecht, The Netherlands: Kluwer Academic Publishers. 615.

²⁸⁹ van Harten, A.M., *Mutation Breeding: Theory and Practical Applications*. 1998, Cambridge, U.K.: Cambridge University Press. 353.

²⁹⁰ Peeters, M.C., K. Willems, and R. Swennen, Protoplast-to-plant regeneration of cotton (*Gossypium hirsutum* L. cv. Coker 312) using feeder layers. *Plant Cell Reports*, 1994. 13: p. 208-211.

²⁹¹ Renfroe, M.H., R.C. Hartwig, and R.H. Smith, *Isolation and fusion of cotton protoplasts*. *Virginia Journal of Science*, 2001. 52: p. 57-65.

²⁹² Evans, D.A. and W.R. Sharp, *Applications of somaclonal variation*. *Bio/Technology*, 1986. 4: p. 528-532.

BXN cotton was planted on only about 1% of the U.S. cotton acres by 1997 but approached 8% in 1999 and 2000. *Bt* cotton was planted on about 12% of U.S. acreage in 1996 and approached 40% in 2000. On a state-by-state basis, peak adoptions of *Bt* cotton were at 80% in Alabama and Florida in this period. RR cotton became the most widely adopted spliced-DNA crop, rising from 4% of planted acreage in its first year of introduction to 54% of U.S. cotton acres in 2000. In 2001, 32% of the U.S. cotton crop was transgenic for glyphosate tolerance and another 24% incorporated both *Bt* and glyphosate (“stacked gene”) tolerance, resulting in 56% of the U.S. cotton crop transgenic for glyphosate tolerance. The peak adoption of glyphosate tolerant cotton lines occurred in 1999 at 94% in South Carolina.^{293, 294}

Possibly the main attraction to growers of transgenic, herbicide-tolerant crops, including cotton, is simplification of weed control efforts. BXN cotton tolerates an “over-the-top” bromoxynil spray at any stage of cotton growth. Bromoxynil provides control of broad leaf weeds only and is most effective when weeds have no more than four true leaves. RR cotton tolerates an “over-the-top” spray of glyphosate when the cotton seedlings are at the four leaf stage or earlier and directed or spot applications later in the season. Glyphosate, unlike bromoxynil, is a general herbicide.²⁹⁵ Thus, BXN cotton and RR cotton have different capabilities, but both provide the grower with a simplified weed control protocol that reduces the need for herbicides that are more persistent than bromoxynil or glyphosate.

Nationally, the period since introduction of herbicide-tolerant cottons has seen a significant reduction in the number of herbicide applications, a reduction in the total amount of active ingredient of herbicides applied, and a shift from soil-applied and more persistent herbicides to herbicides that are applied over the top. The latter herbicides tend to be rapidly degraded, reducing ground water contamination. A part of the reduction in mass of active ingredient herbicides applied can be attributed to the introduction of pyriithiobac (Staple™), a selective broadleaf weed herbicide, introduced in 1995, that can be applied to cotton at any stage of growth and that has a very low application rate. However, U.S. land area planted to cotton in which weed control relies on pyriithiobac has declined since 1997. Acreage where weed control relied on BXN cotton and bromoxynil application increased slightly since 1997. Plantings for which weed control relied on glyphosate and RR cotton increased greatly during this period. These observations suggest that spliced-DNA cotton has been a major contributor to the reduction in numbers of herbicide applications and to the shift away from persistent, sometime soil- and groundwater-contaminating herbicides.²⁹⁶

Origin and Improvement of California Upland Cotton

Upland cotton is generally classified into four types: Acala-which is a long staple type prominent in San Joaquin Valley, cotton-Delta, Plains, and Eastern. Acala cotton is traced to a 1907 introduction from the village of Acala in Chiapas, Mexico. Various selections out of the original Acala were developed in Texas, New Mexico and Oklahoma. USDA researcher W.B. Camp tested Acala cotton lines in the San Joaquin Valley in 1916, and the USDA Shafter Cotton Research Station was established in 1922 under the leadership of Camp. Acala varieties proved to be exceptionally well suited to the San Joaquin Valley. California cotton production has shown higher yields than cotton production elsewhere in the U.S., though not greater than yields in Australia. The California crop also was mechanized earlier than elsewhere

²⁹³ Anonymous, *Acreage, NASS Fact Finders for Agriculture*, <http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bba/acrg0601.pdf>. 2001, National Agricultural Statistics Service, Agricultural Statistical Board, U. S. Department of Agriculture: Washington, D. C.

²⁹⁴ Carpenter, J.E. and L.P. Gianessi, *Agricultural Biotechnology: Updated Benefit Estimates*. <http://www.ncfap.org/reports/biotech/updatedbenefits.pdf>. 2001, National Center for Food and Agricultural Policy: Washington, D.C. p. 46.

²⁹⁵ Anonymous, *UC Pest Management Guidelines. Cotton herbicide treatment table* <http://www.ipm.ucdavis.edu/PMG/r114700311.html#TOP>. 2001, University of California Integrated Pest Management: Davis, California.

²⁹⁶ Carpenter, 2001.

in the U.S. In 1949 about 10% of the cotton crop was mechanically picked, and by 1962 machine harvesting accounted for 90% of the crop.

The one-variety cotton district, created in 1925, resulted in control by the San Joaquin Valley Cotton Board over what cotton seed could be planted, thereby assuring the production of premium cottons with a worldwide demand. The law was later amended to “one-quality” (San Joaquin Valley Quality Cotton District), which allowed growers to experiment with various lines and commercial seed producers to provide seed for testing commissioned by the Cotton Board. Testing occurs over a three-year period at multiple locations and approval depends on a submitted Acala or Pima line equaling or out-performing the corresponding quality standard line.

Spliced-DNA Upland Cotton in California

Adoption of transgenic cotton lines in California has been substantial and rapid, but not as extensive or quick as elsewhere in the U.S.²⁹⁷ The late rains of 1998 were instrumental in bringing transgenic cotton to California.²⁹⁸ The one-quality cotton law made California a very specialized cotton seed market with a delay of three years between the availability of a new cotton variety and its approval, if it is to be approved, by the Cotton Board. The incentive for the seed companies to make investments necessary to bring transgenic cotton to the California market may have been low. An Executive Order from then Governor Wilson allowed seed for early ripening cotton varieties, including transgenic varieties, to be sold and planted for the 1998 season on a one-time basis. The experience of California growers with the new worm resistance and herbicide tolerance traits was favorable, further increasing interest in repealing the 73-year-old one-quality (formerly one-variety) cotton law. However, the Cotton Board approval process continues, allowing growers the option of producing Cotton Board approved cotton. In March 2000, the San Joaquin Valley Cotton Board approved the first

genetically engineered Acala cotton for planting in the San Joaquin Valley Quality Cotton District, two varieties bearing a glyphosate tolerance gene and a third expressing the *Bt* gene.

Table 4 provides data on the introduction of transgenic Upland cottons into California. Although the values from various sources are in only general agreement, the trend toward increased planting of transgenic crops in total is plain. The greatest numerical discrepancy within Table 4 concerns the introduction of *Bt* cotton. According to USDA National Agricultural Statistics Service data,²⁹⁹ which are derived from grower interviews, *Bt* cotton planting increased in 2001 in California, whereas other sources indicate *Bt* cotton is being planted to fewer acres in 2001 compared to 2000. Almost certainly fewer acres of *Bt* cotton were planted in 2001 because the three major insects targeted by *Bt*-expressing cotton, tobacco budworm, cotton bollworm and pink bollworm, are not major insect pests in the San Joaquin Valley and have occurred no more than sporadically in recent years.^{300,301,302} Growers would have little incentive to incur the additional costs of *Bt* technology in the face of reliably low insect pressure. Therefore, it is not the decline in planting of *Bt* cotton in California that is surprising, but rather that there was any significant adoption of *Bt* lines. The explanation lies in the availability of valued traits such as yield potential and early maturation in the *Bt* expressing lines that made those lines attractive in spite of the additional cost of the biotechnology fee (Ron Vargas, personal communication).³⁰³

Table 4 indicates extensive adoption of herbicide-tolerant transgenic cotton in California, with at least 30% of the 2001 crop likely having been derived from BXN and RR genotypes. The national experience in shifts of herbicide use, towards fewer applications and reduced amounts of active ingredient of persistent herbicides, likely is reflected in

²⁹⁷ Vargas, R., R.B. Hutmacher, and S. Wright, *Transgenic cotton: an update and field experience in California*. California Cotton Review, 2001. 58 (April): p. 3-7.

²⁹⁸ Williams, 2000.

²⁹⁹ Anonymous, 2001.

³⁰⁰ Carpenter, 2001.

³⁰¹ Vargas, 2001.

³⁰² Goodell, 2001.

³⁰³ Williams, 2000.

the California experience. There are no wild relatives of *G. hirsutum* (or *G. barbadense*) in California to which spliced-DNA genes might be transferred by cross pollination.

Origin and Improvement of California Pima Cotton

Production of *G. barbadense* cotton in the U.S. currently is limited to the Southwest, but the genetic origins of Pima cotton are global. In the 1780s, fine-linted, extra-long staple (ELS) *G. barbadense* from the Bahamas or Jamaica was imported into South Carolina where it was bred to become an annual known as Sea Island cotton. Sea Island cotton was cultivated in Georgia and the Carolinas within 50 miles of the coast through about 1920. Pima cotton of the U.S. southwest traces its history through Sea Island cotton that was crossed in Egypt with Egyptian Jumel cotton, where it was subject to intensive breeding and selection to yield the cultivar Mitafifi.

Mitafifi was introduced into the southwest about 1900. In that same year, the Colorado River Irrigation Canal was completed and brought water to the Imperial Valley. By 1909, 1,500 of acres of cotton were planted, most to Pima cotton lines brought in from Arizona. Imperial Valley Pima ("Egyptian") cotton acreage increased in succeeding years and peaked in 1920 at 104,000 acres. Pima cotton production almost disappeared by 1930, although it was revived again in the 1950s. In 1989, the San Joaquin Valley, where 98% of all California cotton now is produced, received its first major plantings of Pima cotton. In 2000, 90% of the U.S. production of Pima cotton was derived from California.^{304,305} Table 3 compares the fiber characteristics of genetically improved and unimproved Pima cotton, showing the improved characteristics resulting from conventional breeding efforts, but also that fiber length is less than was achieved with Sea Island cotton. Table 4 includes information on Pima cotton planting in California. Spliced-DNA Pima cotton has not yet been commercialized.

³⁰⁴ Ag-Stats.com, *California Counties Pima Cotton, 1980-2000*. <http://www.ag-stats.com/cotton/californiaP.pdf>. 2001, Ag-Stats.com.

³⁰⁵ CCGA, 2002.

TRANSGENIC FIELD CORN

Industry data suggest that glyphosate-tolerant corn was planted on 5,000 acres out of the total planting of 580,000 acres in California in 1999. In 2000 and 2001, plantings of transgenic corn were on 35,000 acres and 75,000 acres, respectfully. Typically less than half of the corn planted in California is harvested for grain, and probably most of the transgenic corn was used for animal feed. The stated acreages for spliced-DNA, herbicide-tolerant corn in California probably are underestimates. It is reasonable to expect for herbicide-tolerant corn benefits similar to those found for herbicide-tolerant cotton and soybean.^{306, 307} Corn transgenic for the *Bt* gene is of little interest in California because of the low populations of susceptible insect pests. There are no wild relatives of corn in California to which transgenes might be transferred.

TRANSGENIC SQUASH

The second transgenic food crop to receive regulatory approval was spliced-DNA squash engineered to resist a set of viruses that devastate squash production in what otherwise would be good growing areas. Although the virus-resistant squash was cultivated on two to three thousand acres in the U.S. in recent years, only about 10 acres of this commercial production was in California. There probably are no wild squash relatives in California to which transgenes might be transferred from cultivated squash.

PERMITS FOR SPLICED-DNA CROP FIELD TRIALS IN CALIFORNIA AND THE FUTURE OF CROP TECHNOLOGY

Applications to the U.S. Department of Agriculture to perform field tests of transgenic crops are not necessarily predictive of future commercialized crops. However, they are suggestive of the types of cultivars into which investments have been made in constructing the spliced-DNA plant line and completing the permit process, presumably with

³⁰⁶ California Agricultural Statistics Service, *California Field Crop Acreage Report*. <http://www.nass.usda.gov/ca/rpts/acreage/106fldac.htm>. 2001, California Agricultural Statistics Service and National Agricultural Statistics Service: Sacramento.

³⁰⁷ Carpenter, 2001.

an eye towards commercialization. The 321 entries in Table 5 were selected for apparent commercial relevance, neglecting permits that were for plants expressing reporter genes or permits that otherwise appeared to be intended for field tests in support of basic research. Many of the permits covered sites outside of California in addition to California sites. Results from field tests corresponding to the listed permit requests may contribute to advancing the tested gene construction-cultivar combinations to unregulated status and commercial plantings. Test plots described in the permits typically were from one to a few acres, but varied from under 0.1 acre to a few hundred acres.

The Table 5 permits collectively cover 30 crops, indicating both the generality of spliced-DNA technology and its applicability to California crops. The permits describe quality traits such as sugar or solids content or color intensity of the fruit, antioxidant accumulation and altered grain storage protein. However, most of the described traits are production related, including the well-studied and often incorporated insect resistance and herbicide tolerance traits. Other agronomic traits among the subjects of permit requests are resistance against various pathogens, nematode resistance, improved yield or growth rate, delayed senescence, resistance against cold or drought, and parthenocarpy (production of fruit without fertilization). Permit requests do not form a transparent window into plans for future spliced-DNA crops, as indicated by the confidential business information (CBI) notation for several traits. Developers of spliced-DNA crops are even more secretive about the actual genetic constructions under test. Permit requests also come relatively late in the process of developing new spliced-DNA genes and therefore do not reflect what still is in the laboratory.

What can we expect from future spliced-DNA crops in California? If barriers to the use of intellectual property, burdens of regulatory approval, and disapproval from a minority of the public do not prevail, the diversity of California's crop agriculture has much to gain from spliced-DNA technology, but also has some commercial risk. Cotton provides an example of the latter. Low humidity and lack of summer rain in California's prime crop areas give California's growers an edge in the form of reduced disease pressure. Sea Island cotton, with its superior

fiber length, has not been grown in the southeastern U.S. for about 80 years, because insects and pathogens made its production uneconomical. DNA-splicing could install, in Sea Island or other ELS cotton, genes that allow efficient production in the U.S. southeast or elsewhere in the world where production does not now occur, giving additional competition to California's Pima cotton industry. Other transgenic improvements could provide special benefits to California's cotton industry. An aspect of current cotton research is aimed at extending the fiber length for Acala cotton, which is particularly suited to production in the San Joaquin Valley.

California already is the nation's primary producer of health-benefiting foods, in the form of fresh fruits and vegetables. Nature can be improved upon, in the form of enhanced vitamin, flavanoid or mineral content, greater flavor, better texture and other favorable characteristics capable of being conferred by spliced-DNA genes. Crop plants also may be the source of valued medicines, biochemicals, and chemical feedstocks, derived from "niche" crops. There is great room for improved agronomic traits as well. In addition to the agronomic traits represented among the permit applications summarized in Table 5, salt tolerance may be of particular benefit in the irrigated agriculture of California. Transgenic plant lines capable of producing a crop in soil too saline for the corresponding conventional cultivars have been demonstrated.^{308, 309, 310} Tolerance to adverse soil constituents has been extended to a process designated "phytoremediation" in which plants not only grow in contaminated soil but remove and/or metabolize the contaminant, e.g., explosives.³¹¹

³⁰⁸ Rus, A.M., et al., *Expressing the yeast HAL1 gene in tomato increases fruit yield and enhances K⁺/Na⁺ selectivity under salt stress*. *Plant Cell and Environment*, 2001. 24(8): p. 875-880.

³⁰⁹ Zhang, H.X. and E. Blumwald, *Transgenic salt-tolerant tomato plants accumulate salt in foliage but not in fruit*. *Nature Biotechnology*, 2001. 19(8): p. 765-768.

³¹⁰ Zhang, H.-X., et al., *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 of the United States of America*, 2001. 98(22): p. 12832-12836.

³¹¹ Hannink, N., et al., *Phytodetoxification of TNT by transgenic plants expressing a bacterial nitroreductase*. *Nature Biotechnology*, 2001. 19(12): p. 1168-1172.

Although the realities of extensive financial investment, highly skilled people, and hard work needed to create transgenic plants and the realities of legal and social barriers strongly counter the hypothesis, sometimes it appears that the variety and potential benefits of spliced-DNA crops are limited only by imagination.

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	Fiber strength, g/tex	Length, in cm	Fineness (micronaire)
Improved <i>G. hirsutum</i>	33.6	1.16 (2.9)	4.1
Unimproved <i>G. hirsutum</i>	15-20	0.75-1 (1.9-2.5)	>5
Improved <i>G. barbadense</i>	> 38	> 1.5 (3.8)	< 3.5
Unimproved <i>G. barbadense</i>	20-25	1.0-1.2 (2.5-3.0)	5

Table 3. Comparison of improved and unimproved Upland and Pima cottons

Values for “*G. hirsutum* improved” correspond to glyphosate- and bromixynil-tolerant Acala cotton lines Riata RR and BXN Nova (California Planting Cotton Seed Distributors, <http://www.cpcsd.com>).

Other values from;³¹² *G. barbadense* Sea Island cotton may have a fiber length in excess of 2 inches (5 cm).³¹³

“Micronaire” is an inverse measure of the surface area of a cotton sample; the greater the surface area as reflected in resistance to air flow through the fiber sample, the smaller the micronaire number and the finer the fiber.

“Tex” is the weight in grams of cotton fiber of total length 1,000 m; fiber strength is represented by the grams of force required to break 1 tex of fibers.

The three characters indicated in the table headings and fiber color (staining) and trash contamination all influence discounts and premiums paid to cotton producers relative to regional base prices.

³¹² McCarty, 2001.

³¹³ Munro, J.M., *Chapter 18. Lint quality*, in *Cotton*. 1987, Longman Scientific and Technical and John Wiley & Sons: New York. p. 346-381.

Cotton Traits	1999		2000		2001	
	1000's acres	Percentage	1000's acres	Percentage	1000's acres	Percentage
Glyphosate tolerant		(7%)[2%]	126	16% (12%)[21%]	158	24% (35%)
Bromoxynil tolerant		[3%]	63	8% [8.7%]	39	6% (5%)
Total herbicide tolerant	80	13% (7%)	189	24% (17%)	197	30% (27%, 40%)
Insect resistant (Bt)		(7%)[8%]	19	2.5% (3%, 1%)[6%]	7	1% (11%, 0%)
Combined traits		(1%)	58	7.5% (4%, 4%)	29	4.5% (2%, 1%)
Total transgenic	>80	13% (15%)	266	34% (24%, 17%)	233	36% (40%, 37%)
Conventional	<530	87%	509	66%	422	65%
Total upland cotton	610 (620)	100%	775 (770)	100%	655 (620)	100%
Pima cotton	250 (260)		145 (170)		215 (205)	
Total cotton	860		920		870	

Table 4. Estimates of transgenic Upland cotton acreage in California

Total harvested acreage figures are from U.S. Department of Agriculture³¹⁴ and California Cotton Growers Association (Earl P. Williams, personal communication). Other total planted acreage figures, presented in parentheses and not used for calculations, are from the California Agricultural Statistics Service.³¹⁵

Transgenic acreage figures are from the California Cotton Review³¹⁶ and the California Cotton Growers Association. Percentages in bold correspond to these acreage figures.

Percentages in parentheses and underlined are from the National Agricultural Statistics Service;³¹⁷ other percentages in parentheses are from Monsanto Company (Martin Lemon, personal communication) and other industry sources. Percentages in brackets are from the National Center for Food and Agricultural Policy³¹⁸ and are not included in the calculated sums. Accepting the 1999 estimates of 7%-8% *Bt* expressing cotton in California, total transgenic cotton acreage in 1999 would be 122,000-128,000 acres and the percentage of cotton acreage planted to transgenics would be 20%.

All percentages are relative to total California Upland cotton, including Acala. No transgenic Pima cotton was available to growers.

³¹⁴ Anonymous, 2001.

³¹⁵ California Agricultural Statistics Service, 2001.

³¹⁶ Vargas, R., R.B. Hutmacher, and S. Wright, *Transgenic cotton: an update and field experience in California*, California Cotton Review, 2001, 58 (April): p. 3-7.

³¹⁷ Anonymous, 2001.

³¹⁸ Carpenter, 2001.

Crop	Anticipated altered phenotype	Number of permits
alfalfa	glyphosate herbicide tolerance	15
alfalfa	delayed leaf senescence	2
apple	resistance against Lepidoptera	3
apple	altered sugar content	1
barley	heat stable glucanase; phosphinothricin herbicide tolerant	2
barley	wheat glutelin; phosphinothricin tolerant	1
beet	glyphosate herbicide tolerance	5
cabbage	resistance against Lepidopteran larvae	4
cabbage	male sterility; phosphinothricin herbicide tolerant	2
carrot	fungus resistance	2
carrot	glyphosate tolerance	1
carrot	rootknot nematode resistance	1
corn	resistance against Coleoptera	9
corn	resistance against Lepidoptera	4
corn	CBI	4
corn	mixed or stacked genes fungal resistance, insect resistance, herbicide tolerance, mycotoxin degradation, production of novel proteins and others	3
corn	pharmaceutical protein produced	2
corn	male sterility	1
corn	glyphosate tolerance	1
corn	chloroacetanilide tolerance	1
cotton	resistance against Lepidoptera	12
cotton	phosphinothricin herbicide tolerant	5
creeping bentgrass	glyphosate herbicide tolerance	2
cucumber	resistance against specific virus combinations	3
cucumber	glyphosate herbicide tolerance	3
geranium	glyphosate herbicide tolerance	1
grape	resistance against specific viruses	3
grape	improved fruit quality	2
grape	resistance against crown gall bacteria and a virus	1
grape	resistance against crown gall bacteria	1
grape	resistance against fungi	1

Table 5. Permit requests for spliced-DNA field tests in California³¹⁹

³¹⁹ King, D., *Field Test Releases in the U.S. Information Systems for Biotechnology (ISB)*. <http://www.isb.vt.edu/CFDOCS/fieldtests1.cfm>. 2002, Virginia Tech University and USDA Cooperative State Research, Education, and Extension Service: Blacksburg, VA.

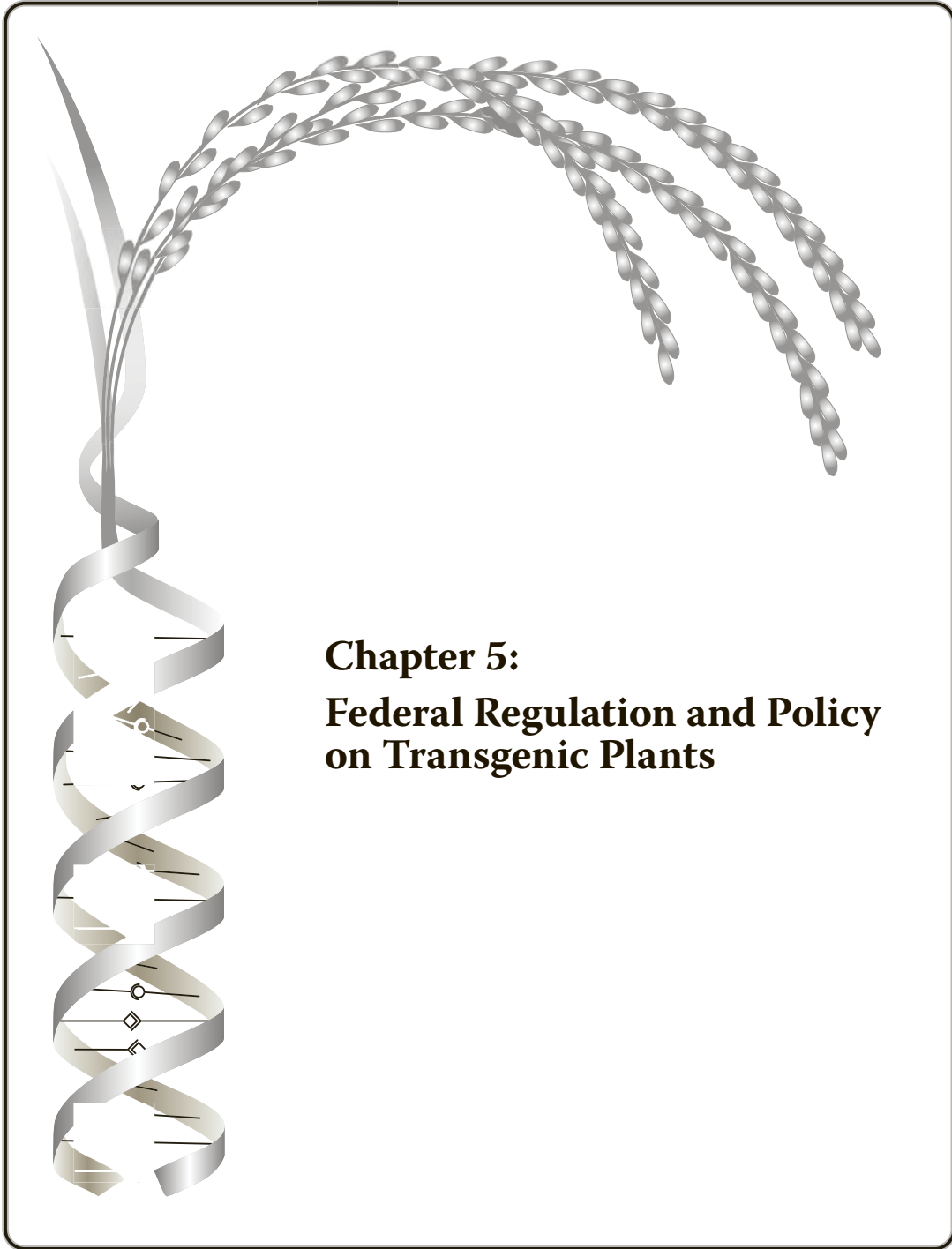
Crop	Anticipated altered phenotype	Number of permits
lettuce	glyphosate herbicide tolerance	29
lettuce	yield or growth rate improvement	4
lettuce	male sterility	3
lettuce	resistance against fungi	3
lettuce	senescence delayed	3
lettuce	resistance against Lepidoptera	2
lettuce	glyphosate tolerance and insect resistance	1
melon	resistance against specific viruses and virus combinations	14
melon	fruit ripening altered	9
melon	male sterility	2
onion	glyphosate herbicide tolerance	1
pea	glyphosate herbicide tolerance	7
pepper	resistance against cucumber mosaic virus	2
persimmon	cold and drought tolerance	2
persimmon	altered fruit ripening	2
petunia	extended flower life and glyphosate tolerance	2
petunia	altered flower color and glyphosate tolerance	2
petunia	glyphosate herbicide tolerance	1
potato	resistance against fungi	3
potato	resistance against specific virus and Colorado potato beetle	2
potato	resistance against specific virus and Colorado potato beetle and glyphosate tolerance	1
rapeseed	seed oils profile altered	4
rapeseed	glyphosate herbicide tolerance	1
rice	glyphosate herbicide tolerance	19
rice	CBI	7
rice	phosphinothricin herbicide tolerance	6
rice	yield increase	2
rice	pharmaceutical protein produced	2
rice	carbohydrate metabolism altered; phosphinothricin tolerance	2
rice	bacterial leaf blight resistance	1
squash	resistance against specific virus combinations	4
strawberry	glyphosate herbicide tolerance	9
strawberry	resistance against several fungi	6

CBI = confidential business information

Table 5. Permit requests for spliced-DNA field tests in California (continued)

Crop	Anticipated altered phenotype	Number of permits
strawberry	extended shelf life	2
strawberry	flowering time altered	2
sunflower	fungal resistance	2
sunflower	resistance against Lepidoptera	2
sunflower	resistance against Lepidoptera and fungi	1
tomato	resistance against specific viruses	7
tomato	carotenoid pigment content altered	6
tomato	resistance against fungi	6
tomato	phosphinothricin herbicide tolerance	5
tomato	glyphosate herbicide tolerance	4
tomato	yield or solids increase	4
tomato	fruit ripening altered	4
tomato	rootknot nematode resistance	2
tomato	parthenocarpy and glyphosate tolerance	1
tomato	parthenocarpy	1
tomato	cold tolerance	1
tomato	chlorophyll increase	1
tomato	antioxidant protein increase	1
walnut	increased adventitious root formation	2
watermelon	parthenocarpy	1
wheat	glyphosate herbicide tolerance	6
wheat	storage protein altered	4
wheat	phosphinothricin herbicide tolerance	1

Table 5. Permit requests for spliced-DNA field tests in California (continued)



**Chapter 5:
Federal Regulation and Policy
on Transgenic Plants**

Chapter 5: Federal Regulation and Policy on Transgenic Plants

John E. Vanderveen, Food and Drug Administration

The federal government has in place a broad and comprehensive approach for policy formation and regulation of development and use of recombinant DNA (rDNA) technology-derived foods as mandated by federal law. These foods are referred to by a number of names and for convenience will be called bioengineered foods or foods derived through rDNA technology in this document. In the United States, three federal government agencies have primary responsibility for regulating bioengineered foods. They are the Food and Drug Administration, the Department of Agriculture, and the Environmental Protection Agency. Other federal agencies have roles relating to policy development, international harmonization, research and information. These roles will be highlighted in the discussion of these areas in the body of this document.

POLICY FORMATION

The federal government has maintained an active process for setting policy on bioengineered foods since the mid 1980s. Recognizing that rDNA technology has the potential for rapidly changing the genetic material of all living organisms and thereby the composition and function of these organisms, the Office of Science and Technology Policy (OSTP) began a coordination process with the key regulatory agencies. The OSTP prepared the basic policy document entitled "Coordinated Framework for Regulation of Biotechnology," and published it in the Federal Register of June 26, 1986 (51 FR 23302). This document is the basis of the current comprehensive policy for insuring the safety of rDNA technology research and foods and other products that have been derived from this technology. This document also established the principles and procedures for coordination among federal agencies for the regulation of rDNA technology.

OSTP prepared and published a second policy statement in the Federal Register of February 24, 1992 (57 Fr 6753) entitled "Exercise of Federal

Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment." These policy guidelines foster a risk-based scientific process for the introduction of products derived from rDNA technology in the environment. This risk-based approach emphasizes examination of the characteristics of the product and its impact on the environment into which it is introduced and used. This is the same risk-based approach that has been applied to all new species derived by other technologies. Thus the policy does not recommend that rDNA technology derived products be given a different assessment because of the process by which the product was created. As will be evident in discussion below, the regulatory agencies have not fully embraced this guidance. For example, foods derived through rDNA technology are automatically subject to requirements for the submission of petitions and/or notifications processes, whereas new foods derived through traditional techniques are not. However, the criteria used by all government agencies to evaluate the data and other information submitted on the safety and impact on the environment of biotechnology derived foods are science based, and the standards for assessing risk are the same as for other foods that are required to undergo premarket notification or petition for approval.

EXISTING REGULATIONS

Regulations of bioengineered foods can be divided into four main areas. Each area is overseen by a different regulatory entity. The first area is concerned with the safety of cultivation and its primary focus addresses the plant pest issues. The second area is concerned with safe use of pesticides including pesticides and pesticide tolerance agents in bioengineered plants. The third area is concerned with the safety of the food products for human and animal consumption, and also addresses the labeling issues. The fourth

area is concerned with the issues of international harmonization and trade.

SAFETY OF CULTIVATION AND ENVIRONMENT

The Animal and Plant Health Inspection Service (APHIS) of the USDA is responsible for protecting the environment and especially the U.S. agricultural environment against pest and disease. Under the Plant Quarantine Act (7 USC 151) and the Federal Plant Pest Act (7 USC 150) APHIS can regulate the importation and interstate movement of plants and plant products that may result in entry into the United States of injurious plant diseases or insect pest. The Plant Protection Act of 2000 (7 USC 7701) has provided additional authority and further guidance to the USDA in the regulation of plant pest and noxious weeds. Using these mandates, APHIS regulates field-testing and the commercial sale of agricultural bioengineered plants through a notification and permit system. APHIS regulations codified in 7 CFR Part 340 cover the introduction of organisms and products altered or produced through “genetic engineering” which are plant pests or for which there is reason to believe are plant pests. “Plant pests” are defined as any organism “which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants.” APHIS maintains a list of organisms (7 CFR Part 340), which are or contain plant pests. A petition can be made to amend the list to either add or delete any genus, species, or subspecies.

A permit application is required for the introduction or fieldtest of a new plant developed using rDNA technology. Under 7 CFR Part 340.4, APHIS prohibits the introduction of any regulated article unless a permit authorizes the introduction. A regulated article includes any organism or any product that has been altered or produced through rDNA technology, that is a plant pest, or for which there is reason to believe is a plant pest. The regulation is intended to prevent the introduction, dissemination, and establishment of plant pests in the United States. APHIS will only authorize a permit if upon evaluation it is determined that the plant poses no significant risk to other plants in the environment and the plant

is considered as safe as traditional varieties of the same species. APHIS has placed major emphasis in granting a permit for movement, importation, and field-testing of a regulated article on measures for identification of the article and its confinement. Guidance on information needed in a permit application include the description of the regulated article, identification of the donor organism, the vector or vector agent used, the intended date of importation, movement, or release, and location of planned release or importation. In addition the application should contain information on how the regulated article differs from the unmodified parent plant, source and location of the parent plant, donor and vector or vector agent, the experimental protocol for the release, description of facilities to be used, the measures to ensure confinement and the plans for disposition of the regulated article. The permit application is required to arrive at APHIS not less than 120 days before the planned importation or release in the environment. APHIS will notify the applicant within 30 days if additional information is needed. If the necessary information is included in the application, APHIS will make a determination on the application within the 120-day period. Provided field trials are successful and the containment of the regulated article is demonstrated, products derived from a regulated article grown under a permit can be distributed commercially as in the case of pharmaceutical compounds.

Certain regulated articles may be introduced without a permit, provided that the introduction meets specified conditions that assure that the environment will not be harmed. These include, among other conditions, a determination that the article is not a noxious weed as defined under 7 CFR Part 360, that the genetic material is stably integrated, that the function of the introduced genetic material is known, its expression does not result in disease in plants, animals, and man, and the encoded products are not intended for pharmaceutical use. Provided specific handling and field trial procedures are met, a notification process can be used to introduce the article either interstate or through importation. Such notification must be submitted at least 10 days prior to interstate shipment and

30 days before importation. APHIS will provide acknowledgement or deny permission within the respective time periods required for each notification. The acknowledgement of notification status allows the applicant to proceed with the plans for importation, movement or release as indicated in the notification. Further the notification process can include the commercial distribution of products derived from the regulated article if included in the notification submission. A denial under the notification procedure is an indication that APHIS has determined that the regulated article is a potential plant pest. Should APHIS find reason to deny permission under the notification procedure, the applicant would still have the opportunity to submit the more detailed application for a permit.

Once a plant has undergone appropriate testing and evaluation, the sponsor can submit a petition for “determination of non-regulatory status.” Upon review of the petition and other relevant scientific information, APHIS can authorize non-regulatory status for the plant and the products derived from the plant. Non-regulatory status allows a plant derived through rDNA technology to be treated like any other plant, i.e., with no limitations on cultivation and commercial distribution (7 CFR Part 340).

The procedures for preparing and submitting petitions as well as definitions of terms are included in 7 CFR Part 340. This regulation also establishes specific requirements for conducting field trials, reporting field trial results, and procedures to be taken upon completion of a field trial. APHIS also has established reporting requirements for accidental or unauthorized release of a regulated article as well as unexpected results from a field trial. All decisions made by the Administrator are placed in the public docket file in the offices of APHIS and in the form of a notice published in the Federal Register.

PLANT-INCORPORATED PROTECTANTS

One of the major uses of rDNA technology in the area of foods has been the development of plants with incorporated protectants. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the substances plants produce for

protection against pests and the genetic material necessary to produce these substances for preventing, repelling, or mitigating any pest are pesticides (7 USC 136-136r). Also included in the definition of pesticides are such substances as plant regulators, defoliants, desiccants, and nitrogen stabilizers. The Environmental Protection Agency (EPA) is responsible under FIFRA for registering pesticides, setting environmental tolerances for pesticides, and establishing exemptions for pesticides in and on crops. With some exceptions, FIFRA requires that pesticides be registered before being distributed or sold in the United States. The exceptions are listed in EPA regulations and include substances used for traditional sanitation processes for many generations.

Registration of a pesticide is accomplished through a petition process. The petition must define the intended application and provide estimates of exposure to the environment including potential exposure to man and animals in the environment. The petition must contain data that the pesticide “will not generally cause an unreasonable adverse effect on the environment.” EPA’s mandate under FIFRA is to protect human health and to safeguard the environment. The definition of environment provided in FIFRA includes “water, air, land and all plants, man and all other animals living therein and the interrelationships which exist among these.” This definition provides broad authority to consider the impact of the use of substances that can be classified as pesticides.

Originally, EPA used the term “plant pesticide” to describe plant substances that protect against pests. In a final regulation published July 19, 2001 in the Federal Register (66 FR 37771), EPA changed the term “plant pesticides” to “Plant Incorporated Protectants.” In addition, EPA created a new part in the Code of Federal Regulations (40 CFR 174) specifically for these substances that occur in plants as a result of being derived through rDNA technology or other techniques that transfer genetic material through other than conventional breeding. Plant-incorporated protectants that are present in plants derived through conventional breeding are exempt from these regulations except the reporting of adverse effects under 40 CFR

174.71. The definition for conventional breeding of plants is “the creation of progeny through either the union of gametes, i.e., syngamy, brought together through processes such as pollination, including bridging crosses between plants and wide crosses, or vegetative reproduction.” The definition specifically excludes: “rDNA [biotechnology], other technologies wherein the genetic material is extracted from an organism and introduced into the genome of the recipient plant through micro-injection, macro-injection, micro-encapsulation, or cell fusion.” Furthermore, the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance must not ever have been derived from a source that is sexually compatible with the recipient plant.

The final regulation published July 19, 2001 is part of a comprehensive regulatory approach that was published as a proposal in the Federal Register on November 23, 1994 (59 FR 60519). This final regulation which became effective on September 17, 2001, sets up the frame work for the total regulatory approach by providing definitions of terms, identifying the products that are subject to the regulation, identifying those products that qualify for exemption, and establishing a requirement for reporting information regarding adverse effects on human health or the environment alleged to have been caused by a plant-incorporated protectant regardless of how the plant was derived. The preamble to this final regulation provides a comprehensive discussion of comments submitted in response to the November 23, 1994 proposal. Additional comments were solicited for some issues, which could not be resolved. However, EPA has indicated other parts of the comprehensive regulation will be finalized in the future. Among those issues are labeling requirements, data requirements, export requirements, experimental use permits, and registration procedures and requirements.

In the interim, the EPA continues to offer consultation to petitioners and recommends that the guidance published in the Federal Register on November 23, 1994 (59 FR 60511) be used for preparing petitions for registration for sale or distribution. This guidance describes information needs under FIFRA for EPA to evaluate a

product under development that contains a plant-incorporated protectant and addresses such topics as: product analysis, exposure assessment, environmental fate analysis, ecological effects, human health effects, and development of resistance to the plant-incorporated protectant.

SAFETY REGULATION OF rDNA BIOTECHNOLOGY DERIVED FOODS

The U.S. Food and Drug Administration (FDA) regulates several aspects of rDNA technology under mandates provided by the Federal Food, Drug and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA). Under the FFDCA, FDA has a mandate to ensure the safety of all foods (except meat and poultry products derived from domesticated animals and domesticated poultry) that enter interstate commerce. The FDA also is responsible for the safety and efficacy of all pharmaceutical products and animal feeds sold in the U.S.

The FDA has broad authority to regulate all foods that are derived from new food crops, whether derived through conventional breeding, hybridization, cross breeding, or other procedures such as rDNA technology. Every firm or individual that produces whole foods or food ingredients is required by law to ensure the safety of foods and food ingredients that they introduce into commerce. The FFDCA prohibits the adulteration of food under section 402 of the act (21 USC 342) and misbranding of food under section 403 of the act (21 USC 343). In particular, a food is deemed adulterated if it contains certain poisonous and deleterious substances (21 USC 342(a)(1)). The act also requires that all food additives as defined by section 201(s) of the act (21 USC 321(s)) be approved by the FDA before they are marketed (sections 409 and 402 of the act (21 USC 348(a) and 342(a)(2)(C)). With some exceptions, the FFDCA defines a food additive as any substance which is not generally recognized as safe (GRAS) by qualified experts for its intended use that becomes a component or otherwise affects the characteristics of a food (21 USC 321(s)). The FDA has the authority under section 304 of the act (21 USC 334) to seek sanctions against foods that do not comply with the requirements of the act. The

agency carries out sanctions by securing a court order to seize the product. Sections 302 and 303 of the act (21 USC 332 and 333) authorize the agency to seek an injunction against, or criminal prosecution of, those responsible for introducing non-compliant foods into the market place.

To fulfill its mandate to assure the safety of new foods, the FDA (in consultation with other federal regulatory agencies) studied the potential of increased safety risk of foods derived through rDNA technology. The FDA has asserted in the May 29, 1992 "Statement of Policy: Foods Derived From New Plant Varieties" (57 FR 22984) that a nonpesticidal substance introduced into a food by way of breeding is a food additive if the substance is not generally recognized as safe (GRAS) within the meaning 21 USC 321(s). Further, the FDA reasoned that "because of the greater range of sources of substances that can be introduced into plants using rDNA technology, there is a greater likelihood that some of the new substances will be significantly different from substances that have a history of safe use in food or may otherwise not satisfy the GRAS standard (66 FR 4709)." However, FDA stated in 1992 (57 FR 22990) and reaffirmed in 2001 (66 FR 4709) that transferred genetic material can be presumed to be GRAS. The FDA also reaffirmed the 1992 conclusion that "there is unlikely to be a safety question sufficient to question the presumed GRAS status of the proteins (typically enzymes) produced from the transferred genetic material, or substances produced by the action of the introduced enzymes (such as carbohydrates, fats, and oils), when these proteins or other substances do not differ significantly from other substances commonly found in food and are already present at generally comparable or greater levels in currently consumed foods." Finally, the FDA concluded that if through rDNA technology or other biotechnology there is an introduction of genetic material that results in the modified food containing substances that are significantly different from, or are present in food at a significantly higher level than counterpart substances traditionally consumed in food, then the new substance may not be GRAS and may require regulation as a food additive (57 FR 22990 and 66 FR 4709).

On May 29, 1992, the FDA provided policy guidance to the industry on appropriate steps to be taken prior to the marketing of a new variety of plant or product of a plant derived through rDNA technology (57 FR 22984-23005). To facilitate the implementation of guidance, the FDA provided a series of flow charts that posed critical questions directed to scientific issues of safety and nutrition. A summary flow chart shown in Figure 4 illustrates the major areas of concern to the agency. The guidance document contains additional flow charts that elaborate on the areas of concern. The answers to these questions provide an assessment of the need for consultation with the FDA and may indicate a need for further investigation of safety and/or nutrition issues. This assessment process is designed to answer risk based issues that include: the presence of toxicants; the potential for known food allergens to be present in the food that were not previously found; the safety and bioavailability of new proteins contained in the product; the levels and bioavailability of essential nutrients normally found in the traditional food; and the structural identity, levels, and nutritional value of modified carbohydrates, fats, and other energy yielding compounds. To further facilitate the consultation process, the FDA in June 1996 issued guidance to the industry on procedures for these consultations. This guidance is available on the agency's web site <http://vm.cfsan.fda.gov>. In the 1992 and 1996 guidance, the FDA encouraged all developers to consult with the agency prior to marketing a new rDNA derived variety even if no concerns were raised by the questions posed by the flow chart. To date, the FDA believes that all developers of new products that have been commercialized have consulted with the agency. Lists of the completed consultations are found in Tables 6 and 7.

On January 18, 2001, the FDA published a proposed rule in the Federal Register (66 FR 4706) that would require the submission to the agency of data and information regarding "plant derived bioengineered foods" that would be consumed by humans and animals. FDA proposed that this submission be submitted at least 120 days prior to the commercial distribution of such food. In addition, the proposed rule makes a strong recommendation for presubmission consultation.

During a presubmission consultation, the FDA encourages the discussion of safety, nutrition and other issues that are likely to be associated with the bioengineered food. Such a consultation would be made public unless the requestor can demonstrate that the criteria for exemption from disclosure in CFR 21 20.61 are satisfied.

The FDA proposed rule of January 18, 2001 included a detailed list of required information that must be contained in the premarket notification. The first section shall be a synopsis of information presented in the presubmission consultation. This synopsis would be a concise document that describes the bioengineered food in a manner that can be easily recognized by an informed consumer. Next, the agency has proposed that the notifier include a detailed discussion of any prior or ongoing evaluation of the bioengineered plant or food derived from such a plant by the USDA/APHIS and EPA. The FDA is also proposing that the notifier inform the FDA as to whether the bioengineered food is or has been the subject of review by any foreign government and, if so, provide the status of that review. These requirements permit the agency to exchange information between regulatory agencies and be aware of evaluations, identification of concerns, and the need for interagency consultation during the review process. Also the disclosures concerning other agency reviews will provide the FDA with the need for enforcement of pesticide tolerances and other enforcement requirements that the FDA must fulfill.

The proposed rule would also require a detailed discussion of the method of development used to obtain the bioengineered food. This must include the characterization of the parent plant including the scientific name, taxonomic classification, mode of reproduction, and pertinent history of development. Next, the notifier must describe the vector used in the transformation of the parent plant and a characterization of the genetic material intended for introduction into the parent plant. The description must include the number of insertion sites, the number of gene copies inserted at each site, information on DNA organization within the inserts and information on potential reading frames that could express unintended

proteins in the transformed plant. The proposal would also require notification on any newly inserted genes that encode resistance to an antibiotic.

Major considerations in assessing the safety of a new food are increases in levels of some substances found in foods or the presence of new substances not found in the traditional or comparable food. The FDA has proposed that the notification include data or information about substances introduced into, or modified in, the food. The notifier would be required to provide data or other information about the identity, function and the levels of new substances found in the bioengineered food. The notifier also would be required to provide estimates of dietary exposure to these substances for population segments. In the case of any new protein substances introduced into a food, the notifier would have to provide information about the potential that this protein will be an allergen. A more general discussion will be required on the safety of all other new non-protein substances that are found in the bioengineered food.

Finally, the FDA is requiring any general information about a bioengineered food that would effect the nutritional value of diets in which the food would be used or have some change in functional property that would require special labeling. First the notifier would be required to provide justification for selecting a particular food or foods as comparable food to which the bioengineered food will be compared. Then the notifier would be required to provide data or information comparing the composition and characteristics of the bioengineered food to those of comparable foods. The notifier would be required to place emphasis on significant nutrients normally found in the comparable food, naturally occurring toxicants, and anti-nutrients that would impact nutritional value or safety. A discussion of any intended changes in composition shall also be included. The notifier would be required to conclude with a narrative discussion that explains his or her basis for concluding that the bioengineered product is as safe as the comparable food and that bioengineered food is otherwise in compliance with all applicable requirements of the Food Drug and Cosmetic (FD&C) Act.

The FDA is proposing that an initial evaluation of the notice would be accomplished by the agency within 15 days to determine if the notice appeared to contain all elements required. If the notification appeared to be complete, the Agency would then announce a filing decision. After the filing is made, the agency is proposing to respond to the notifier within 120 days. The agency foresees several possible responses to the filed notification. They include a letter that would extend FDA's evaluation of the notification; a letter that the notification does not provide a basis for the bioengineered food is as safe as the comparable food or is otherwise lawful; a letter that FDA had no further question concerning the notifier's view that the bioengineered food is as safe as a comparable food and is otherwise lawful; or that the notifier has withdrawn the notice. It should be noted that this notification process does not constitute a process of approval of a bioengineered food by the agency. The responsibility for the safety of the bioengineered food remains with the notifier and the agency can challenge the safety of the food in the event that new data become available which raise safety concerns.

The FDA has included proposed regulations regarding foods that would be used in animal feed as part of the January 18, 2001 Federal Register notice (66 FR 4724). In general, the requirements for submission of a premarket notification are the same as those for human food. However, such a notification must address the relevant issues that pertain to each of the species for which the bioengineered food is likely to be used as a food in the diet.

LABELING OF BIOENGINEERED FOODS

Most food labeling in the United States is mandated under the Food Drug and Cosmetic (FD&C) Act. The labeling of foods regulated under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act are exceptions. Although these acts are administered by different agencies of the federal government, the labeling requirements of all these acts are very similar. Since the labeling of all rDNA technology derived foods marketed to date and for the foreseeable future are regulated

under the FD&C Act, it is appropriate to limit discussion to the labeling mandated by that act.

There are no special requirements for the labeling of rDNA technology derived foods. These foods are subject to the same laws and implementing regulations as all other food regulated by the FDA. In addition, certain requirements established by case law must also be observed. In order to describe the labeling requirements, some brief discussion of definitions in the FD&C Act are essential. Labeling is defined in the FD&C Act as "written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article" [sec. 201 (n)]. Therefore, labeling includes, but is not limited to, the label that is physically attached to the immediate container of food in package form [sec. 201 (k)]. Physical attachment or proximity of material to the product is not required for material to be considered labeling for the purposes of the statute. In a 1948 case, the U.S. Supreme Court found that a booklet containing information about a product that was sold separately was nevertheless labeling for purposes of the statute because the product and the booklet "were parts of an integrated distribution scheme" [Kordel v. United States, 335 US 345 (1948)]. Understanding of the legal definition of labeling is important to the enforcement of the FD&C Act and its implementing regulations.

GENERAL REQUIREMENTS

The FD&C Act calls for certain basic information that must be provided on the label of all packaged food regulated by the Food and Drug Administration (FDA). These include: a statement of identity [sec. 403(i)(1)]; a list of the ingredients used to manufacture the food [sec. 403(i)(2)]; the name and address of the manufacturer, packer, or distributor [sec. 403(e)(1)]; declaration of net quantity of contents [sec. 403(e)(2)]; and the listing of nutrient content [sec. 403(q)]. For some foods, there are additional requirements such as declaring that the food is an imitation of a traditional food [sec. 403(c)] and declaration of the presence of artificial flavors, colors, and chemical preservatives when used [sec. 403(k)]. The Act also provides the FDA with specific authority to

require label information in the case where in the course of evaluation of a new food additive it is determined that a statement is needed for the safe use of a food [sec. 409(c)(1)(A)].

FALSE OR MISLEADING STATEMENTS

In general once the fundamental label requirements above have been met, a food manufacturer, processor, packer, or other party responsible for the label is generally at liberty to make use of labeling space in a manner that they deem fit. However, this liberty to use the remaining available space is only allowed if the label or labeling is not false or misleading. Under sec. 403 (a)(1) of the act, a food is misbranded if its labeling is false or misleading in any particular. If a statement, picture or other representation of any product is false or misleading, the food is misbranded regardless of the importance of the representation to the consumer. The Supreme Court has held that it is not necessary to show that anyone was actually misled or deceived, or that there was any intent to deceive, in order to find the product is misbranded under the FD&C Act [United States v. 95 Barrels-Cider Vinegar, 265 US 438 (1924)]. The finding that a label or labeling is false or misleading is not limited to the patently false claims. Statements that, while not false, are misleading are also prohibited. For example, labeling a broccoli as cholesterol-free suggests that only that particular broccoli is cholesterol-free, while ordinary broccoli is not cholesterol-free. The claim is misleading since ordinary broccoli does not contain cholesterol. The FD&C Act explicitly prohibits a claim that states the absence of a nutrient unless the nutrient is usually present in the food. [sec. 403(r)(2)(A)(ii)(I)]. To avoid being misleading, the FDA permits the claim “broccoli, a cholesterol-free food” (CFR 101.13).

FINDING OF MATERIAL FACT

Labeling statements may be misleading not only by what is said, but may also be misleading by what is not said. In sec. 201(n) of the Act, the FDA is charged not only with determining whether the labeling is misleading because of what “representations (are) made or suggested by statement, word, design, device, or any

combination thereof, but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which might result from the use of article to which the labeling relates under the conditions of use prescribed in the labeling thereof, or under such conditions of use as are customary or usual.” The law, thereby, provides the agency the opportunity to require additional labeling in those situations where there is failure to reveal material facts. There is neither a statutory nor a regulatory definition of “material fact” nor have the courts elaborately defined the term. Determinations of whether or not a fact is material are made on a case-by-case basis. Generally, if a new or modified food were significantly different from its conventional counterpart in composition, nutritional value, safety, or a functional property, the difference in the food would be considered a material fact. For example, if a new processing technique resulted in a significant decrease in the nutrient content or a change in composition or intended use of a food, a label statement would be required to inform consumers of that material fact. Through the years, there have been a large number of precedents on which the FDA has relied for guidance. All these determinations were based on either economic or public health needs of the consumer. The agency has cited other factors such as religious, cultural, or environmental reasons as supporting elements in these decisions, but has not relied on such reasons as the sole basis of a determination.

Often the remedy for a determination of material fact is to establish an accurate and meaningful name for the food. Under section 403(i) of the Act, the food must bear its common or usual name. If a new food differs from a traditional food in composition, nutritional value, or functional properties valued by consumers, then there is a material fact that must be delineated in the name of the product. In recent years, the agency has allowed the use of modifications to the traditional, common or usual name of a food to facilitate advising consumers of significant differences in new products and thus avoid misbranding of the food.

In the case where a standard of identity or a common or usual name was promulgated for the traditional food, the law required that a new product not meeting these standards must be labeled as an imitation [sec. 403(c)]. The intent of this section of FD&C Act passed in the 1930s was to alert consumers to an inferior product and promote honesty and fair dealing. In 1973, the FDA narrowed the definition of imitation when the new product was judged to be nutritionally equivalent to the traditional product and allowed the product to be called a substitute provided the name of the product clearly indicated the difference to the traditional product [21CFR 103(e)]. The FDA undertook this rulemaking effort because technology had advanced the ability to make alternative products that were as or more wholesome than the original product but would have to be labeled as imitation. Consumers generally perceived the term imitation as inferior. This regulation which narrowed the definition of imitation was challenged and upheld several times, most significantly in *Federation of Homemakers v. Schmidt*, 385 F. Supp. 362(D.D.C. 1974), *aff'd*, 539 F.2d 470 (D.C. Cir. 1976). Also see *National Milk Producers Federation v. Harris*, 653 F.2d 339 (8th Cir. 1981); and *Grocery Manufacturers Association v. Gerace*, 755 F.2d 993 (2nd cir. 1985).

CONSTITUTIONAL CONSTRAINTS

The major consideration of the labeling of food in the United States is the constraints that are inherent in the Constitution of the United States. In the American legal system, the Constitution is paramount. Therefore, all statutory labeling requirements, the implementing regulations, and labeling policies must satisfy constitutional requirements. The major constitutional consideration in matters of food labeling is the First Amendment constraint of government labeling regulation. The First Amendment of the U.S. Constitution states: "Congress shall make no law.... Abridging the freedom of speech."

Until recent years, government restrictions on advertising or labeling were considered purely economic regulation that was not covered by the First Amendment. In the early 1940s, the Supreme Court had excluded commercial speech from the coverage

of the First Amendment. However, in the mid 1970s, coverage under the First Amendment was extended to include commercial speech [*Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, 425 US 748 (1976)]. Commercial speech is commonly defined as speech in any form that advertises a product or service for profit or for any business purpose, or as speech that proposes a legitimate business or commercial transaction.

In 1980, the Supreme Court held that commercial speech is protected by the First Amendment and set forth a four-pronged test for determining permissible regulation of commercial speech [*Central Hudson v. Public Service Com'n of N.Y.* 447 US 557 (1980)]. Under the *Central Hudson* decision, the Supreme Court ruled the government may restrict commercial speech if (1) the speech is either misleading or concerns an unlawful activity, or if (2) the asserted government interest in support of restriction is substantial, (3) the restriction directly advances the government's substantial interest, and (4) the regulation is not more extensive than is necessary to serve that interest. Under this decision, government restrictions on misleading commercial speech are not subject to the second, third, and fourth prongs of the ruling. In general, the prohibition of misleading labeling is the objective of most of the specific labeling requirement of the FD&C Act, as are most FDA regulations of voluntary labeling statements.

Of equal importance to constraints on regulation is the First Amendment's protection of the right not to speak. The constitutionally protected right not to speak is clearly established in Supreme Court precedent [*Harper & Row, Publishers, Inc. v. National Enter.* 471 US 539 (1985); *Wooley v. Maynard*, 430 US & 05(1977)]. In a 1943 decision, the Supreme Court indicated that compelling someone to speak involuntarily is protected by the constitution to a greater extent than preventing speech [*West Virginia State Bd. of Ed. v. Barnette*, 319 US 624 (1943)]. The regulation of food labeling involves both the commercial speech and the compelled speech doctrines. To date, the courts have not addressed a compelled commercial speech doctrine. Nevertheless, the current food law that requires the existence of material fact as a basis for requiring compelled commercial speech tends to strike a balance between commercial speech and consumer

needs for information. This supposition seems to be born out in the case of the rBST controversy.

In the early 1990s, the FDA approved the treatment of dairy cows with recombinant bovine somatotropin (rBST), an rDNA biotechnology-derived hormone that increases a cow's milk production. This approval met with significant controversy because of social issues rather than demonstrated safety concerns although some were alleged. In New England states, the concerns were particularly acute because it was seen as a threat to the economic viability of the region's small family run dairy farms. The State of Vermont enacted a law requiring that milk from cows treated with rBST bear a mandatory label disclosure. The constitutionality of this state labeling requirement was challenged in court and the State of Vermont sought to justify its law on the basis of the consumer's right to know, not on health or safety concerns. However, the U.S. Court of Appeals for the Second Circuit stated that Vermont's limited justification was understandable, as "the already extensive record in the case contains no scientific evidence from which an objective observer could conclude that rBST has any impact on dairy products." Using the criteria from the Central Hudson case, the Second Circuit concluded that "consumer curiosity alone is not a strong enough state interest to sustain the compulsion of even an accurate, factual statement." Thus, without a material fact that distinguishes the characteristics of milk from rBST-treated cows from the milk of non-treated cows, there was not a substantial government interest to justify the labeling requirement. As a result, the Vermont disclosure law was unconstitutional in the court's finding.

The existing statutes, implementing regulations, and case law have a profound effect on what labeling can be required and what voluntary labeling can be permitted for bioengineered foods. The FDA has required that some bioengineered foods have specific information of the labeling to reveal material facts about the food. Some examples are high oleic acid soybeans, rice with added vitamin A, and tomatoes with extended shelf life. In these cases, the agency required that these products be named accordingly. In all these cases, the nutritional composition or functional properties were sufficiently different to warrant labeling information to inform consumers. While the

FDA has required special label where differences exist, the agency has taken the position that under existing law special labeling for a bioengineered food cannot be required in the absence of material fact under section 201(n) of the FD&C Act. On the other hand, a manufacturer or distributor can voluntarily disclose information indicating whether a food has or has not been developed using biotechnology provided that information is truthful and not misleading. To assist industry in avoiding the use of false or misleading statements, the FDA on January 18, 2001 issued draft guidance entitled "Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering." This guidance is found on the FDA web site <http://www.cfsan.fda.gov/~dms/biolabgu.html>. For example, a cornmeal product derived through biotechnology that is not found to be materially different from traditional cornmeal can make the statement: "This product contains cornmeal that was produced using biotechnology." A second example of a voluntary statement is for a tomato that may have been derived through biotechnology: "Some of our growers plant tomato seeds that were developed through biotechnology to increase crop yield." In both of these examples, the information is totally voluntary however the information must be true. Voluntary claims can also be included with the information required as a mandatory disclosure. For example, the disclosure statement required for high oleic acid soybean oil may be incorporated into a broader statement as follows: "This product contains high oleic acid soybean oil from soybeans developed using biotechnology to decrease the amount of saturated fat."

The FDA provided special guidance for claims made that a food was not derived through biotechnology so called "free" claims. The agency asserted that the use of the acronym "GMO Free" was unacceptable for several reasons. Consumers generally do not understand the meaning of acronyms and, therefore, whole words should be used. It was also pointed out that the use of the term modified was not technically accurate because the claim had to be made in the context of biotechnology. The agency also points out that the word organism is inappropriate for use with higher plants. Lastly, the agency points out that the word "free" means zero unless the word

has been defined with a threshold, which has not been done. For foods that are not derived through bioengineering, the FDA provided several examples of acceptable claims such as: “We do not use ingredients that were produced using biotechnology.” “This oil is made from soybeans that were not genetically engineered.” “Our tomato growers do not plant seeds developed using biotechnology.” In each of these claims, the process is being described not the content of the product. The agency warned that there must not be an implied claim for superiority such as safer, higher quality or more nutritious, and claims for “free” must apply for all ingredients in a product. Finally, some process of substantiation must back claims that a product does not contain ingredients that were derived through biotechnology. This can be through a process of validated testing or a process of segregation. The process of segregation would typically involve documentation of source through certification or affidavits and certification of special handling throughout the transportation chain.

The EPA and the USDA have not at this time required any special labeling for plants derived through rDNA technology. However, both agencies are likely to consider such requirements in the future. The USDA would likely require special labeling in the event animal or poultry produce are offered for sale that are derived through biotechnology and differ substantially from traditional products. EPA has raised the possibility of requiring special labeling for plant-incorporated protectants that would be consistent with requirements for the labeling of pesticides.

PROPOSED FEDERAL CERTIFICATION

The introduction of rDNA technology derived foods into the world market has brought an urgent need for the development of detection methods, the establishment of improved quality standards, and the need for standardization and validation of testing procedures. The USDA Grain Inspection, Packers and Stockyards Administration (GIPSA) on November 30, 2000 published an Advanced Notice of Proposed Rulemaking in the Federal Register that requested comments on 11 questions relating to that agency’s role in modern biotechnology. These questions were designed to assess the needs for standards for Identity Preservation (IP) or other marketing

systems that facilitate market development. The GIPSA noted the rise in number of companies and organizations engaged in reviewing and verifying the performance of food company IP systems and asked if the USDA should have a role in the accreditation of these certifying companies and organizations. The GIPSA also indicated that it was developing a program for accrediting commercial and public laboratories for the analytical detection of grains and oilseeds derived from biotechnology, and asked if this should be expanded to other crops. The agency also asked if it should provide, for a fee, direct product certification for crops derived from biotechnology based on an audit-based quality assurance process. The agency asked if it should provide direct analytical detection services and certification for crops derived from biotechnology. Actually the agency’s laboratories were heavily involved in the testing of the extent of Starlink™ contamination of the general corn supply. Finally, the GIPSA asked if the USDA should establish grades and standards for crops derived from biotechnology as it does for traditional commodities. It is clear that the GIPSA has already taken major steps in methods for detecting foods derived through rDNA biotechnology in the market place. With growing international constraints on the movement of these foods, it is likely the USDA will need to expand current efforts in the standards and detection area.

INTERNATIONAL COORDINATION AND STANDARDS

The use of rDNA technology for the development of new foods and drugs has been met with a diverse response from countries around the world. Even the regulatory approach taken for drugs and foods are often very different within the same country. A few countries have taken action to not allow the use of foods derived through the use of biotechnology. Many countries have no regulation that effect the development and production of foods derived from biotechnology. Still others such as those in the European Community (EU) require approval of each food before marketing and have required labeling of foods that contain more than 1.0% of ingredients obtained from biotechnology-derived plants. This diversity in approach to regulation from country to country has resulted in pressure from industry to foster increased harmonization of food standards

and guidelines of the United Nations, the World Trade Organization (WTO) and the Organization for Economic Cooperation and Development (OECD).

The United Nations (UN) is the focus of most of the international agreements and standards setting activity. The coordination work is carried out by specialized agencies that are manned by an administrative staff recruited from member nations. These specialized agencies organize committees made up of representatives from member countries on technical subject area. It is the practice that when a committee is established, a member nation is selected to chair the committee, to manage the committee's business and to host the committee meetings. It should be pointed out that the UN specialized agencies do not have enforcement authority and that its standards and agreements only have an effect on a country if and when that country elects to adopt them. Three specialized agencies of the UN have significant roles in the efforts in standard setting and international agreements in the food safety and quality area. They are the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and the United Nations Environmental Program (UNEP). All three agencies coordinate their activities with other agencies to some extent, but since individual nations can choose to belong to specific committees and control the committee activities there is often some duplication. The FAO has responsibility for managing the International Plant Protection Convention (IPPC). The IPPC was established under the FAO in 1951; however, the IPPC had its roots in several international agreements dating back to the late 1800s. There are more than one hundred governments that are members of the Convention. The IPPC is a focal point for international cooperation and technical exchange of information. It also fosters national and regional plant protection organizations. The IPPC is one of three international reference standard bodies incorporated into the WTO Agreement on the application of the Sanitary and Phytosanitary (SPS) Agreement. IPPC was selected as the authoritative international body for plant pest and disease standards. In 1997, a revision of the IPPC was approved by member nations at a FAO Conference. The revision included changes that reflect the IPPC's new role as an authoritative standard setting body relative to SPS measures. The 1997 revision also

established an Interim Commission on Phytosanitary Measures (ICPM) that will serve until the revision is approved by member nations and a permanent commission is formed. The ICPM is charged with carrying out the IPPC's tasks associated with SPS measures and other administrative tasks until the new revision is approved by member nations. In 1999, the ICPM formed an Expert Working Group on issues surrounding the creation of standards in relation to organisms derived through biotechnology, biosafety, and invasive species. Part of the charge to the working group was to explore the relationship of IPPC to the Cartagena Protocol. In April 2001, ICPM established a new Expert Working Group on Living Modified Organisms (LOM). The LOM Expert Working Group is charged with the development of detailed standard specifications for LOMs to guide the implementation of the Convention on Biodiversity. The USDA's Animal and Plant Health Inspection Service is the lead agency for representing the U.S. in the work of IPPC.

The major international activity concerning standards for foods derived from rDNA technology is centered in the committees of the joint FAO/WHO Codex Alimentarius Commission (CAC). This organization was established as a UN program in the early 1960s and has been highly regarded for its activities in harmonizing food standards internationally. It has 165 member countries that represent 98% of the world population. The CAC has two committees and a separate time limited task force that are involved in issues that are related to foods derived from rDNA biotechnology. They are the Codex Committee on General Principles (CCGP) chaired by France; the Codex Committee on Food Labeling (CCFL) chaired by Canada; and the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology. The U.S. Codex Office (located in USDA) coordinates the U.S. participation in the Codex activities. This office is the focal point for all incoming and out going communication. A United States Codex Policy Steering Committee and a United States Codex Technical Steering Committee composed of all government agencies that have an interest in the Codex process provide oversight for the U.S. participation Codex. Members of the committee include representatives from the U.S. Trade Representative (USTR), the Department of State, the Department of Commerce, the Food

and Drug Administration, the Centers for Disease Control, the Environmental Protection Agency, USDA's Food Safety and Inspection Service, USDA's Foreign Agricultural Service, USDA's Animal and Plant Health Inspection Service and other USDA agencies. Representation on delegations to specific Codex committees is decided by jurisdictional responsibility. Usually a delegate from the agency having the most interest in a particular Codex committee will head the delegation. That agency will also solicit input from all other government agencies and non-government organizations in preparation of the U.S. position on the issues before a Codex committee.

The major role of the CCGP is to provide guidelines and standards to all Codex Committees for use in the performance of their mission. The CCGP is involved in biotechnology because the committee is preparing a draft Codex document entitled *Working Principles for Risk Analysis* which contains the concept of precaution. The objective of this document is to establish the principles for conducting risk analysis that will be used as the standard by Codex committees. The CCGP has reached agreement on two aspects of the risk analysis principles, those relating to risk assessment and those relating to risk communication. However, the committee is in major disagreement over the element of risk management. The EU members are demanding that a "precautionary principle" be included in addition to the traditional definition for risk management. The United States' position is that there is always precaution as part of good science. The traditional approach to risk assessment and risk management that has been an essential element of the regulatory system for food and environmental safety for decades includes precaution and, therefore, a separate precautionary principle is unnecessary. The United States believes that the use of the terminology "precautionary principle" is a way for countries to manipulate risk analysis results and thereby open the process to protectionism. The proposed draft *Working Principles for Risk Analysis* was the subject of considerable debate at the Codex Commission meeting in June 2001. In an attempt to find a compromise, the commission adopted the following position: "When there is evidence that risk to human health exists but scientific data are insufficient or incomplete, the Commission should

not proceed to elaborate a standard, but should consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence" (Item 81 of The Report of 24th Session of Codex Alimentarius Commission, Geneva, 2-7 July 2001). Following the Commission meeting, the Joint FAO/WHO Food Standards Program Secretary revised the Proposed Draft Working Principles for Risk Analysis and sent it to governments and interested international organizations for further comment (CL 2001/24-GP July 2001). This is a major issue for biotechnology because the EU has not approved the importation of new biotechnology foods for some time and has indicated their intention to apply the precautionary principle to foods derived biotechnology which would likely continue to inhibit product approvals and continue to block trade. The EU maintains that its population is demanding that these foods need to undergo additional risk analysis using a more cautious approach.

The Codex Committee on Food Labeling (CCFL) is one of the most important Codex committees. The labeling of food has a major impact on its movement in the world markets. A working group of 33 members has been assigned the task of developing a draft standard for labeling foods derived from biotechnology. There is significant difference in positions of the United States, Canada, and some other countries versus the position of the EU and other countries. The U.S. favors only labeling those biotechnology-derived foods that present a potential safety risk (i.e., allergens) or that have a significant difference in nutritional value or functional property compared to the traditional food. The EU favors labeling all foods derived through biotechnology that contain a detectable amount of new DNA or protein derived from rDNA biotechnology. A third position presented by Norway and India would require the labeling of all foods derived through biotechnology. Currently, the working group is attempting to further refine these options.

The Codex Ad-hoc Intergovernmental Task Force on Food Derived from Biotechnology is a task force with a mandate to operate for four years. The task force is chaired by Japan. The task force is attempting to obtain agreement on three items: 1) Broad principles for risk analysis of biotechnology foods;

2) Guidelines for the food safety assessment of foods derived from rDNA plants; and 3) Guidelines for the food safety assessment of foods derived from rDNA microorganisms. Originally the prospects for quick agreement on the “principles” seemed problematic since some delegations were asking for consideration of extensive procedures for traceability as a part of the process. Nations that produce large amounts of the grain that is offered for sale on the international market objected to the impracticality and significant cost of providing extensive traceability information on routine bases. However, during the third session of the Codex Ad-hoc Intergovernmental Task Force on Foods Derived from Biotechnology (March 2002), an agreement was reached stating that “the tracing of products for the purpose of facilitating withdrawal from the market when a risk to human health has been identified or to support post-market monitoring” may be needed. Further, the Task Force “recognized that there are other applications of product tracing and these applications should be consistent with the provisions of the SPS and TBT Agreements” (<http://www.codexalimentarius.net/biotech/en/ra-tbt.htm>).

The United Nations Convention on Biological Diversity was signed by the United States in 1993 the same year it went into effect. The U.S. Senate has not ratified the treaty so the United States is still not a party to the convention. The objectives of the convention are: “the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of utilization of genetic resources” by all nations involved. The protocol is a legally binding agreement on parties. Its purpose is to protect the environment from risks posed by transport across boundaries of living modified organisms (LOMs) created by modern biotechnology. The protocol will become effective when 50 countries that are party to the agreement ratify it. Currently nine of the 89 signatories have ratified the protocol. For changes in the number of countries that have ratified the protocol, see web site www.biodiv.org/biosafety. When ratified, the protocol requires that bulk shipments of LOM commodities that are intended to be used as food for human food or animal feed such as corn, soybeans, and wheat would have to be accompanied by documentation stating that such shipments may contain living modified organisms

that are not intended for intentional introduction into the environment. The protocol requires that more restrictive Advanced Informed Agreement procedures will apply to other LOM such as seeds, and live animals that are intended for intentional introduction into the environment for reproductive purposes. The exporter of such LOMs must provide detailed information to each importing country in advance of the first shipment. The importing country has 270 days to conduct a scientific risk-based assessment after receiving the notification of intent to export. After the importing country has completed the risk assessment, it has 15 days to post the decision on the Internet-based Biosafety Clearinghouse.

The World Trade Organization (WTO) came into being on January 1, 1995, after more than eight years of negotiations among leading world trading partners. Two of the agreements that were established by the Uruguay Round trade negotiations that established the WTO have a direct impact on trade involving foods derived from rDNA technology. These are the SPS Agreement and the Agreement on Technical Barriers to Trade (TBT Agreement). The SPS Agreement recognizes the right of member countries to “take sanitary and phytosanitary measures necessary for the protection of human, animal and plant health.” However, these agreements require that such measures must be made on the basis of sound science to avoid the use of SPS measures being used as a technical barrier to trade. The agreements recognize standards developed by the International Office of Epizootics (IOE), IPPC and Codex as the basis for assessing the evidence on which SPS measures are justified. IOE, IPPC and Codex standards were accorded this status based on the recognition that they were created using sound scientific data. By implication, these standards are important to settling trade disputes. To date, the WTO has not created a working party on biotechnology. The USTR is the lead agency representing the U.S. trade interest. Other government agencies provide technical expertise for setting policy and assisting in negotiations.

The final organization that has a potential role in the standard setting for foods derived from rDNA biotechnology is the Organization for Economic Cooperation and Development (OECD). The

purpose of OECD is to assist foster marketing systems, promote trade liberalization and to assist developing nations in building strong economies. One of the projects that OECD has carried on for many years has been the maintenance of an internationally recognized system for certification of seed purity and content. Many seed companies have relied on this organization's standards for assuring their products in the world market. Currently this organization is the focal point for assuring seeds claimed to be non-biotechnology derived. There are ongoing negotiations to define the level of contamination that should be permitted from seeds containing DNA derived from biotechnology in the seeds purported to be non-biotechnology derived and the methods to be used to certify these seeds.

FEDERAL RESEARCH AND MONITORING OF BIOTECHNOLOGY

The federal government's role in biotechnology-related research is both significant and diverse. The National Institutes of Health continues as a major source of funding support for academic and other independent basic research in the area of rDNA technology. Although most of this research is not directed at development of new species of plants that are used for food, the new techniques developed as part of this research have been the basis for most of the advancements in the field of biotechnology. The Agriculture Research Service has a major plant-breeding program that has been the source of many new species of cultivated food crops in the U.S. for more than a century. In recent years, a significant amount of these resources have been dedicated to using rDNA technology to develop plants that resist disease and pest, reduce the needs for weed control and increase yield. The USDA Cooperative Research, Education, and Extension Service administers the biotechnology-risk assessment program as well research programs in gene mapping, sequencing, and biotechnology applications.

The cultivation and marketing of biotechnology-derived crops has had a significant impact on the marketing of traditional varieties of agricultural commodities. The USDA Economic Research Service (ERS) conducts research on the economic impact of the production of rDNA technology derived

crops. The ERS also develops cost estimates for implementing new systems for marketing traditional non-biotechnology commodities such as those associated with identity preservation (IP). Currently several agencies are developing chemical techniques for detection of inserted DNA and the new proteins derived from the added DNA in plant products. Current methods lack sufficient low detection limits and speed to meet efficient use in IP applications.

Finally, a substantial effort exists within the USDA, EPA, and FDA in monitoring the impact of the introduction of foods derived through rDNA technology in the food supply. These efforts include monitoring the impact on the environment, assessing changes in the nutritional quality of the food supply, investigating claims of allergenicity, and evaluating herbicide and pesticide periodic performance.

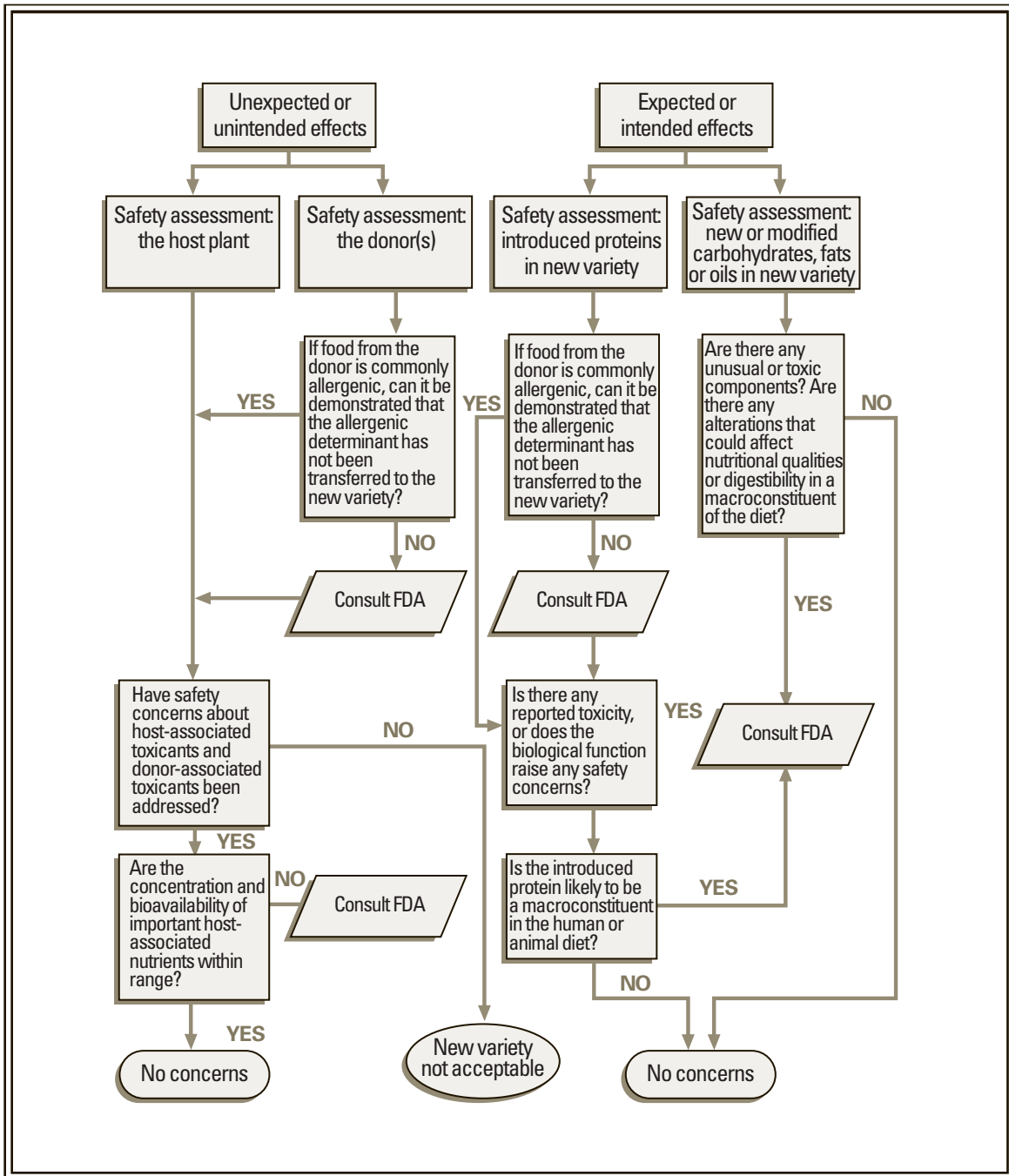


Figure 4: Safety assessment of new varieties: summary

Source: Food and Drug Administration, 1992.

Year/Firm	New Variety	Trait gene and source
2000		
Aventis	Male-sterile corn	The barnase gene from <i>Bacillus amyloliquefaciens</i> .
1999		
Agritope, Inc.	Modified fruit-ripening cantaloupe	S-adenosylmethionine hydrolase gene from <i>Escherichia coli</i> bacteriophage T3.
BASF AG	Phytaseed canola	The phytase gene from <i>Aspergillus niger</i> var van Tieghem.
Rhone-Poulenc Ag Co.	Bromoxynil-tolerant canola	The nitrilase gene from <i>Klebsiella pneumoniae</i> subsp. <i>ozaenae</i> .
1998		
AgrEvo, Inc.	Glufosinate-tolerant soybean	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
	Glufosinate-tolerant sugar beet	Phosphinothricin acetyltransferase gene from <i>S. viridochromogenes</i> .
	Insect-protected and glufosinate-tolerant corn	The <i>cry9C</i> gene from <i>Bacillus thuringiensis</i> (Bt) subsp. <i>tolworthi</i> and the bar gene from <i>Streptomyces hygroscopicus</i> .
	Male-sterile or fertility-restorer and glufosinate-tolerant canola	The male-sterile canola contains the barnase gene, and the fertility-restorer canola contains the barstar gene from <i>B. amyloliquefaciens</i> . Both lines have the phosphinothricin acetyltransferase gene from <i>S. viridochromogenes</i> .
Calgene Co.	Bromoxynil-tolerant/insect-protected cotton	Nitrilase gene from <i>Klebsiella pneumoniae</i> and the <i>cryIA(c)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
	Insect protected tomato	The <i>cryIA(c)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
Monsanto Co.	Glyphosate-tolerant corn	A modified enolpyruvylshikimate-3-phosphate synthase gene from corn.
	Insect- and virus-protected potato	The <i>cryIIA</i> gene from <i>B. thuringiensis</i> sp. <i>tenebrionis</i> and the Potato Leafroll Virus replicase gene.
	Insect- and virus-protected potato	The <i>cryIIA</i> gene from <i>B. thuringiensis</i> sp. <i>tenebrionis</i> and the Potato Virus Y coat protein gene.
Monsanto Co/Novartis	Glyphosate-tolerant sugar beet	The enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4, and a truncated glyphosate oxidoreductase gene from <i>Ochrobactrum anthropi</i> .
Pioneer Hi-Bred	Male-sterile corn	The DNA adenine methylase gene from <i>E. coli</i> .
University of Saskatchewan	Sulfonylurea-tolerant flax	Acetolactate synthase gene from <i>Arabidopsis</i> .
1997		
AgrEvo, Inc.	Glufosinate-tolerant canola	Phosphinothricin acetyltransferase gene from <i>S. viridochromogenes</i> .
Bejo Zaden BV	Male-sterile radicchio rosso	The barnase gene from <i>B. amyloliquefaciens</i> .
Dekalb Genetics Corp.	Insect-protected corn	The <i>cryIA(c)</i> gene from <i>B. thuringiensis</i> .
DuPont	High-oleic-acid soybean	Sense suppression of the GmFad2-1 gene which encodes a delta-12 desaturase enzyme.
Seminis Vegetable Seeds	Virus-resistant squash	Coat protein genes of Cucumber Mosaic Virus, Zucchini Yellow Mosaic Virus, and Watermelon Mosaic Virus 2.
University of Hawaii/ Cornell University	Virus-resistant papaya	Coat protein gene of the Papaya Ringspot Virus.

Source: Food and Drug Administration, 2000.

Table 6: Foods derived from new plant varieties derived through rDNA technology: final consultations under FDA's 1992 policy

Year/Firm	New Variety	Trait gene and source
1996		
Agritope Inc.	Modified fruit-ripening tomato	S-adenosylmethionine hydrolase gene from <i>E. coli</i> bacteriophage T3.
Dekalb Genetics Corp.	Glufosinate-tolerant corn	Phosphinothricin acetyl transferase gene from <i>S. hygrosopicus</i> .
DuPont	Sufonylurea-tolerant corn	Acetolactate synthase gene from tobacco, <i>Nicotiana tabacum</i> cv. <i>Xanthi</i> .
Monsanto Co.	Insect-protected potato	The <i>cryIIIA</i> gene from <i>B. thuringiensis</i> .
	Insect-protected corn	The <i>cryIA(b)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
	Insect-protected corn	The <i>cryIA(b)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
	Glyphosate-tolerant/insect-protected corn	The enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4 and the glyphosate oxidoreductase gene from <i>O. anthropi</i> in the glyphosate tolerant lines. The <i>cryIA(b)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> in lines that are also protected.
Northrup King Co.	Insect-protected corn	The <i>cryIA(b)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
Plant Genetic Systems NV	Male-sterile and fertility-restorer oilseed rape	The male-sterile oilseed rape contains the barnase gene from <i>B. amyloliquefaciens</i> ; the fertility restorer lines express the barstar gene from <i>B. amyloliquefaciens</i> .
	Male-sterile corn	The barnase gene from <i>B. amyloliquefaciens</i> .
1995		
AgrEvo Inc.	Glufosinate-tolerant canola	Phosphinothricin acetyltransferase gene from <i>S. viridochromogenes</i> .
	Glufosinate-tolerant corn	Phosphinothricin acetyltransferase gene from <i>S. viridochromogenes</i> .
Calgene Inc.	Laurate canola	The 12:0 acyl carrier protein thioesterase gene from California bay, <i>Umbellularia californica</i> .
Ciba-Geigy Corp.	Insect-protected corn	The <i>cryIA(b)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
Monsanto Co.	Glyphosate-tolerant cotton	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4.
	Glyphosate-tolerant canola	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4.
	Insect-protected cotton	The <i>cryIA(c)</i> gene from <i>B. thuringiensis</i> subsp. <i>kurstaki</i> .
1994		
Asgrow Seed Co.	Virus-resistant squash	Coat protein genes of Watermelon Mosaic Virus 2 and Zucchini Yellow Mosaic Virus.
Calgene Inc.	<i>FlavrSavr</i> TM tomato	Antisense polygalacturonase gene from tomato.
	Bromoxynil-tolerant cotton	A nitrilase gene isolated from <i>Klebsiella ozaenae</i> .
DNA Plant Technology Corp.	Improved-ripening tomato	A fragment of the aminocyclopropane carboxylic acid synthase gene from tomato.
Monsanto Co.	Glyphosate-tolerant soybean	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4.
	Improved-ripening tomato	Aminocyclopropane carboxylic acid deaminase gene from <i>Pseudomonas chloraphis</i> strain 6G5.
	Insected-protected potato	A <i>cryIIIA</i> gene from <i>B. thuringiensis</i> sp. <i>tenebrionis</i> .
Zeneca Plant Science	Delayed-softening tomato	A fragment of the polygalacturonase gene from tomato.

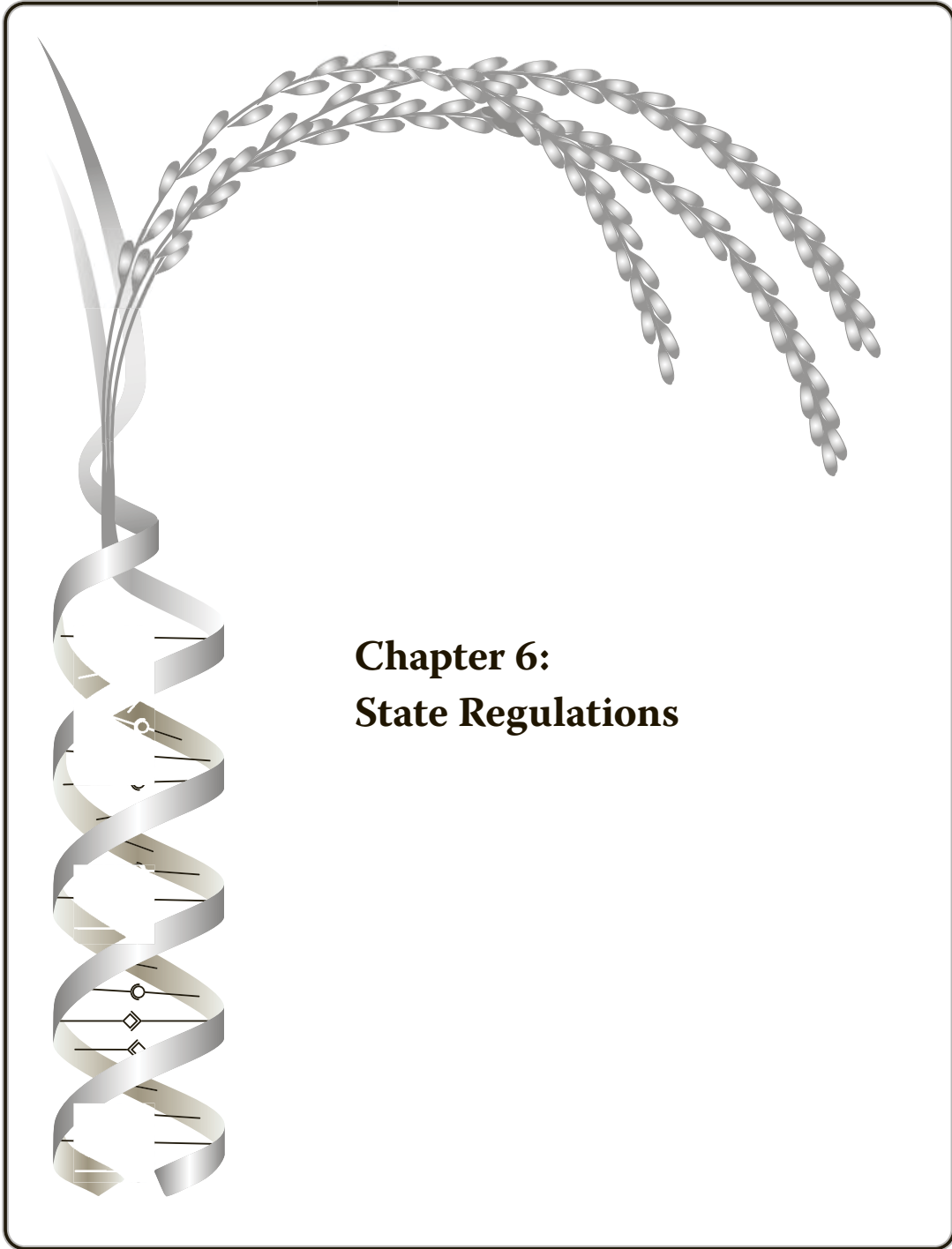
Source: Food and Drug Administration, 2000.

Table 6: Foods derived from new plant varieties derived through rDNA technology: final consultations under FDA's 1992 policy (continued)

Year/ Firm	New variety	Trait gene and source
2001 Dow AgroSciences	Insect-protected and Glufosinate-tolerant corn	Cry1F protein from <i>Bacillus thuringiensis</i> Phosphinothricin acetyltransferase (PAT) from <i>Streptomyces viridochromogenes</i>
2000 Monsanto	Glyphosate-tolerant corn	5-Enolpyruvylshikimate-3phosphate synthase (EPSP) from <i>Agrobacterium</i> sp. Strain CP4

Source: Food and Drug Administration, 2001.

Table 7. Foods from new plant varieties derived through rDNA Technology: final consultations under FDA's 1992 policy



**Chapter 6:
State Regulations**

Chapter 6: State Regulations

David Luscher and John Steggall, California Department of Food and Agriculture

SUMMARY

The State of California, like most states, has deferred to the federal government for regulation of biotechnology products. In 1985, a state task force was formed to review state and federal regulations regarding modern biotechnology. The task force recommended that no special state regulations were justified for genetically engineered (GE) products. In 1994, a task force subcommittee recommended against specific labeling for biotechnology-derived foods. Thus, food derived from GE sources is regulated in California under the same rules that govern conventional food industries. Some state agencies do request and review technical information regarding genetic modifications for research and experimental use permits.

BACKGROUND

In 1984, the California Legislature adopted Assembly Concurrent Resolution 170 "... to promote the biotechnology industry, while at the same time protecting public health and safety and the environment..." Accordingly, in 1985, the Governor's Interagency Task Force on Biotechnology was formed. The Task Force looked at public health and safety issues concerning biotechnology and reviewed the adequacy of state and federal statutes for regulating products derived from biotechnology. In 1986, the Interagency Task Force released the report, *California's Biotechnology Permits and Regulations - A Description*.³²⁰ This report was designed to help biotechnology companies identify and comply with existing state regulations already in place for conventional products which would also apply to any new biotechnology products (see Appendix for summary of selected departments with existing areas of oversight into which genetically engineered food and agricultural products would fall).

³²⁰ Interagency Task Force on Biotechnology, State of California, *California's Biotechnology Permits and Regulations - A Description*, September 1986.

The Interagency Task Force's Food Labeling Subcommittee considered the issue of whether biotechnology foods (biotech foods) should be labeled. The Food Labeling Subcommittee Report of June 1994³²¹ made the following findings and recommendations:

1. It is unnecessary to require special labeling of biotech foods. Such labeling would not provide protective or material health and safety information for the consumers. Mandatory labeling could result in added expense to consumers without added benefits of meaningful information or improved food safety.
2. Biotech foods should be labeled according to the same criteria used for labeling all foods sold in the marketplace, i.e., on the basis of consumers' need for information about nutritional content, safety, and use of the product.
3. Special labeling of biotech foods must be required when there is a potential health risk about which the consumer needs to be informed, such as allergenicity. The determination of such labeling requirements must be made on an individual product basis.
4. Negative labeling of traditional foods (e.g., milk is claimed "from cows not treated with rBST") should be discouraged. Such labeling implies the food has a special attribute which it does not have. Negative labeling may mislead and confuse consumers, and provides no additional public health protection.
5. The Task Force should establish a Subcommittee to investigate options and alternatives for a state-sponsored consumer education program on food biotechnology.

³²¹ Interagency Task Force on Biotechnology, State of California, *Food Labeling Subcommittee Report*, June 1994.

CURRENT STATUS OF STATE REGULATORY SYSTEMS FOR GENETICALLY ENGINEERED FOOD PRODUCTS RELEASED INTO THE MARKETPLACE

Once genetically engineered (GE) crops, raw agricultural commodities, and/or food products have been evaluated by the federal government and released into the marketplace, they are regulated in California in an identical manner as their already existing conventional counterparts which may fall under some form of regulation by state agencies. (Those conventional counterparts include organisms [and their derived products]) bred or obtained via sexual or asexual reproduction which is generally constrained by limits on species reproductive compatibility.) The hazards and/or quality issues associated with GE products reviewed and released by the federal government are considered to be no different than (or equivalent to) existing counterpart conventional products. The state requires no special labeling, special permits, technical review of genetic modification production methods nor any special tracking of movement, sale or planted acreage. The state relies on the federal government's review to identify and mitigate any specific technical "production" related or genotypic issues. The state regulates GE products and their derivatives by phenotype (expressed physical characteristics) based on criteria previously established to determine the safety, quality, or wholesomeness of their conventional counterparts.

GENETICALLY ENGINEERED CROPS CONTAINING PLANT-INCORPORATED PESTICIDES AND HERBICIDE TOLERANT CROPS

The California Department of Pesticide Regulation (CDPR) regulates pesticide use in the state, including both United States Environmental Protection Agency (USEPA) registered and experimental products. Products of biotechnology that come under the CDPR's regulatory oversight include genetically engineered microbial pesticides, and possibly certain pesticidal plants that have been engineered to contain foreign insecticidal toxins (e.g., *Bacillus thuringiensis* toxins). These plant-incorporated pesticides do

not require registration by CDPR, but their use and required USEPA registration are currently under review by an internal working group to examine what CDPR's activity should be in this area.

CDPR also registers USEPA approved uses of herbicides in order for them to be used in California on herbicide-tolerant crops that have been genetically engineered for tolerance. CDPR review consists of evaluating the expanded use of the herbicide, not the genetically engineered crop plant, per se.

Research Permits/Authorizations

The California Department of Food and Agriculture (CDFA) reviews and provides comments to the United States Department of Agriculture (USDA) on forwarded applications for federal permits to bring new GE organisms or crops into the state for research purposes. In this case, the federal permit applications are reviewed by CDFA to confirm that the GE organisms or crops meet current California plant quarantine requirements. CDFA has statutory authority to regulate and mitigate plant pest risks to the state's agricultural production systems. In reviewing research permit applications, CDFA considers special conferred attributes related to genetic modification to determine if they present a risk of (invasiveness/weediness) becoming an agricultural pest. The existence of wild relatives capable of interbreeding/cross pollination and the proximity of potentially impacted agricultural production are also considered. The CDFA review is based primarily on the identified phenotype of the GE organism or crop under consideration. Currently, CDFA does not have the in-house technical expertise (nor often the confidential business information) to do an in-depth critique of the genetic engineering methods, such as viral coat proteins used or rDNA insertion locations etc., and what this may mean as far as presenting any special environmental hazards.

The CDFA review of USDA research permit applications considers only the plant pest risks of moving the identified organism phenotype into a specific location within the state for experimentation. CDFA submits comments to the USDA regarding plant pest risks identified

or proximity to sensitive production areas and makes recommendations as to the safe guards or mitigating actions believed appropriate. USDA permit evaluation staff also visit the proposed research site as part of the permit application review process. The USDA then considers CDFA comments, on-site USDA staff evaluations and their own review of the permit application often in consultation with the USEPA and the United States Food and Drug Administration (USFDA) in their determination to grant or deny a research permit application. Evaluation of such issues as possible impacts to the natural ecosystem, human health risks, and nutritional quality associated with biotechnology and resultant products are the domain of USDA, USEPA and USFDA.

Any person or institution proposing an experimental use of a genetically engineered microbial pesticide must also obtain authorization from CDPR for pesticides not registered in California. Treated commodities from these field trials cannot enter channels of trade unless a federal food tolerance or exemption has been established by USEPA. Releases of new genetically engineered microbial pesticides may require a USEPA Experimental Use Permit (EUP). Pesticide registrants experimenting on “property under their control” (e.g., research farms) are exempt from CDPR research authorization requirements. The Agricultural Commissioner of the county where research is to be conducted is notified. The Pesticide Registration Evaluation Committee in CDPR is also notified of the proposed experiment.

Informational requirements for CDPR Pesticide Research Authorization are identical to those of the USEPA EUP. Information includes:

- Taxonomic analysis
- Recombinant techniques used
- Methods for measuring product purity
- Temperature requirements and survival limitations
- Infectivity and pathogenicity to non-target organisms

- Environmental fate, including growth and survival on non-target species
- Competition with other organisms in the environment
- Survival in soil, air, water (as applicable)
- Capability to spread in air, water, via animals, etc. (as applicable)
- Any earlier data submitted to, or required by, USEPA
- Acute toxicity data

APPENDIX

Select listing of departments with existing areas of oversight into which genetically engineered food and agricultural products would fall:

California Department of Health Services (CDHS)

CDHS regulates foods, food additives, or food stuffs; basically any part of a food intended for human consumption. CDHS normally acts in conformance with established federal standards. CDHS does not directly license food additives not approved by USFDA.

Under both California and federal law, producers, processors, and marketers of foods have the primary responsibility to assure that the foods they supply are safe for consumption. In California, the CDHS has the responsibility of providing oversight to assure that foods sold are safe and that any new food products meet established food safety standards. Several program areas within CDHS must act cooperatively to meet the objective of assuring and improving food safety.

Food and Drug Branch (FDB) enforces the laws intended to prevent adulterated, misbranded, or falsely advertised foods from being sold. To do that, the FDB performs inspections of food manufacturers, investigates consumer complaints, evaluates safety information, and provides educational materials to consumers, community groups, other agencies, and industry on food safety issues. The FDB responds to public health emergencies involving foods by enforcing the removal of unsafe products from the marketplace and issuing consumer warnings.

Division of Communicable Disease Control provides expert consultation and conducts epidemiologic investigations of food-borne disease outbreaks involving infectious or toxigenic microorganisms, and also some well-recognized food-borne diseases involving naturally occurring toxicants found in some foods.

Division of Environmental and Occupational Disease Control provides expert consultation and conducts epidemiologic investigations of food-borne disease outbreaks involving naturally occurring food-associated toxicants, toxicants that may be introduced or are not removed through processing (including pesticides and non-pesticides), nutritional deficiencies, allergic diseases, etc. This division also is concerned with assessing occupational health needs of agricultural, food manufacturing, and food service workers.

California Department of Pesticide Regulation (CDPR)

CDPR regulates all pesticides used in the state including both federal Environmental Protection Agency registered and experimental products.

Pesticide Registration Branch evaluates and registers pesticides for sale in the state.

Pesticide Enforcement Branch responsible for taking action against pesticide misuse, unregistered products offered for sale in the state and mislabeled products.

California Department of Food and Agriculture (CDFA)

Veterinary Biologics and Licensing Program issues a license to firms that manufacture veterinary biologics (vaccines, diagnostic reagents and kits and blood transfusion products) for use only within California (The USDA, Center for Veterinary Biologics in Ames, Iowa issues a license to veterinary biologic firms that distribute nationally.) The Staff Veterinarian in charge of the Biologics Program reviews and approves outlines of production, manufacturing facilities, applications for permits to conduct field trials, permits to bring organisms, vectors, or other biologic specimens into California, and inspects facilities for compliance with applicable regulations and production standards.

Feed, Fertilizer and Livestock Drug Program registers “biotics”, soil and seed inoculants containing live microbes to improve soil fertility and/or plant vigor. If a new biotic is proposed for registration to allow sale within the state, the program will require efficacy data which supports label claims of increased soil fertility (nutrient availability) or increased plant vigor. There is currently no regulatory oversight by CDFA on experimental field trials of biotics for use on agricultural production lands.

Milk and Dairy Foods Control Branch ensures that milk, milk products, and products resembling milk products are safe and wholesome, meet state and federal composition requirements, and are properly labeled.

Plant Health and Pest Prevention Services (PHPPS) requires a permit to move restricted, quarantined or exotic plant materials, insects, animals, and microbes into California. USDA-Animal and Plant Health Inspection Service does the initial permit review and then forwards to affected states for comment/input. The Special Assistant for Permits and Regulations is the person within PHPPS responsible for reviewing these permit applications. Other department staff are involved in the permit review as appropriate. Researchers wishing to move experimental GE organisms between contained facilities in California must provide movement notification to PHPPS.

California Department of Fish and Game (CDFG)

CDFG requires aquaculture facility registration including marine aquaculture (exempts fish/aquatic plants in closed systems for ornamental use only such as koi and tropical). To register a facility, CDFG evaluates the species to be cultivated and provisions to ensure they will not escape into state waters. Species not currently established in California (exotic) and prohibited species require special authorization.

The use of state-owned tidelands for aquaculture is regulated by Fish and Game Commission by lease agreements. An application for lease is obtained from CDFG (note: marine fish and shell fish cultivated for human consumption are also regulated by the California Department of Health Services).

Office of Environmental Health Hazard Assessment (OEHHA)

Part of the California Environmental Protection Agency, OEHHA is the lead agency within the state government for the assessment of health risks posed by hazardous substances. OEHHA provides other government agencies with risk assessment guidelines and scientific information to assist them in their regulatory decisions. The core scientific programs for OEHHA are divided into four sections: Reproductive and Cancer Hazard Assessment, Pesticide and Environmental Toxicology, Air Toxicology and Epidemiology, and Hazardous Waste Toxicology.

California Department of Industrial Relations (CDIR)

CDIR is responsible for enforcement of job safety and workplace health standards and may have regulatory impact on biotechnology industry.

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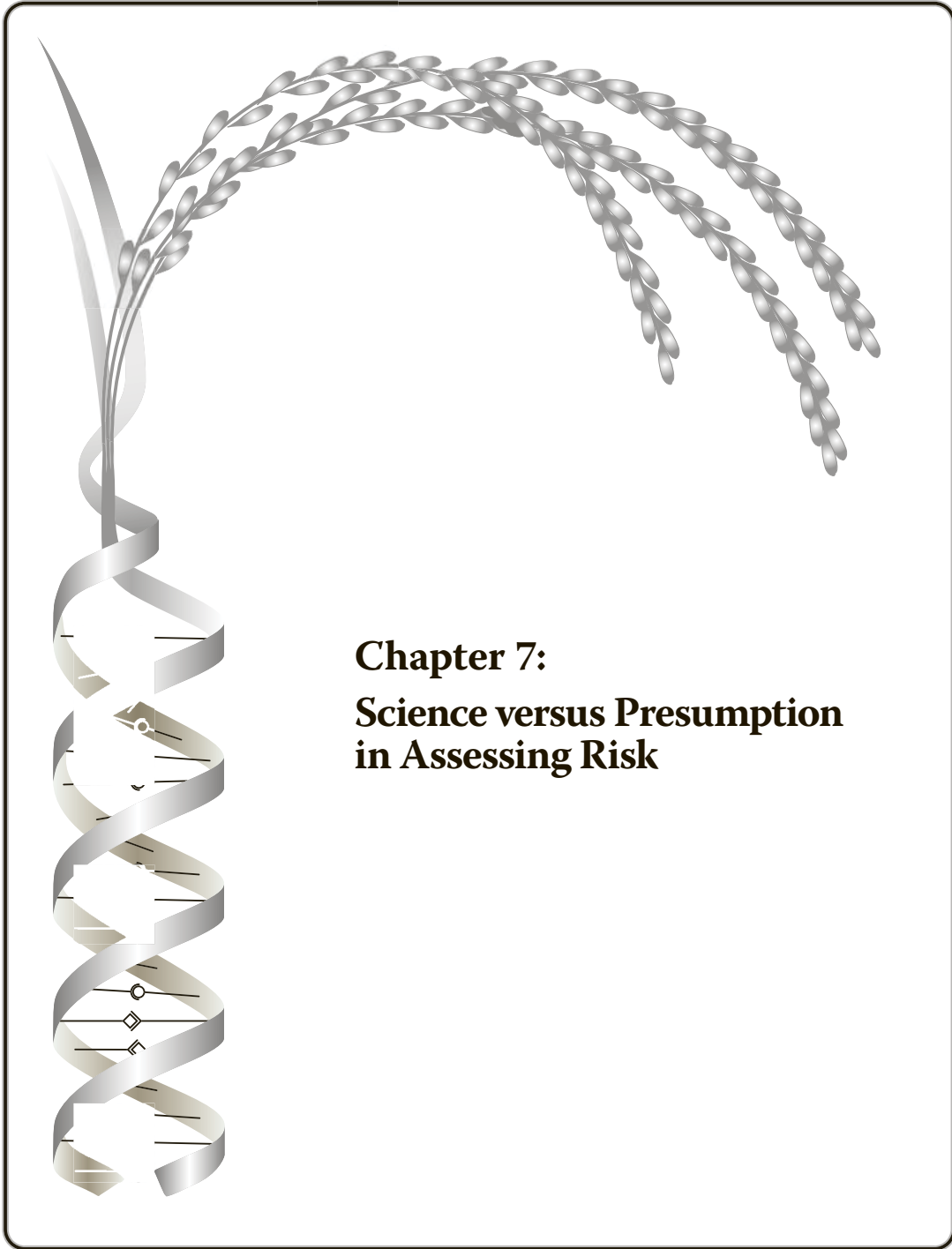
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**Chapter 7:
Science versus Presumption
in Assessing Risk**

Chapter 7: Science versus Presumption in Assessing Risk

Henry I. Miller, Hoover Institute And Gregory Conko, Competitive Enterprise Institute³²²

Consumers benefit in a myriad of ways from the development of new technologies and products, including lower prices, greater choices, and improved quality. But the possibility that a given innovation will pose risks to public health or the environment cannot be ignored; therefore, the challenge of government regulation is to permit beneficial new products to undergo testing and enter the marketplace, while limiting or mitigating serious hazards. How to accomplish this most effectively and efficiently has been the subject of much deliberation and debate.

Environmental and public health activists long have clashed with scholars and risk-analysis professionals over the appropriate regulation of various risks. Underlying the controversies about various specific technologies and products – such as chlorinated and fluoridated water, pesticides, hormones in livestock, and recombinant DNA-modified (gene-spliced) foods – has been a fundamental, almost philosophical, question: How should regulators, acting as society’s surrogate, approach risk in the absence of certainty about the likelihood and magnitude of potential harm?

Traditional regulatory approaches for many classes of new products have focused on an evaluation that considers both the magnitude and likelihood of plausible health or environmental harms on one hand, and expected benefits on the other. That assessment would then, at least in part, dictate the choice of an oversight regime. That regime would then be applied to individual products: Those whose harms are expected to exceed benefits are judged to pose an unreasonable risk and are not permitted to enter the market, whereas products whose benefits are expected to exceed harms are permitted.

But foresight is imperfect, and disproportionate harms from marketed products do sometimes occur. Ostensibly in order to reduce the likelihood and impact of such occurrences, for more than a decade proponents of a highly risk-averse approach to regulation have advocated the use of the “precautionary principle,” which they argue will reduce the risk of such harm.

There is no widely accepted definition of the precautionary principle, but its most common formulation is that governments should implement regulatory measures to prevent or restrict actions that raise even conjectural threats of harm to human health or the environment as long as there is incomplete scientific evidence as to the potential significance of these dangers. Its advocates argue that such a “precautionary approach” to risk regulation is necessary for many new technologies and products (and even for many that are decades old). However, support for precautionary regulation is perhaps nowhere more zealous than in the case of recombinant DNA technology, or gene splicing (also sometimes referred to misleadingly as “genetic modification,” or “GM”) applied to agricultural, food and environmental products. Whether the term “precautionary principle” is used or not, this risk-averse approach provides the foundation for much of the current regulation of gene-spliced products. For that reason, the subject warrants extensive discussion.

The use of the precautionary principle is sometimes represented euphemistically as “erring on the side of safety,” or “better safe than sorry” – the idea being that the failure to regulate risky activities sufficiently could result in severe harm to human health or the environment, and that “over-regulation” causes little or no harm. But this latter assumption is highly misleading.

Although potential risks should be taken into consideration before proceeding with any new activity or product, whether it is the siting of a

³²² This manuscript builds on earlier, shorter papers by the same authors: Miller, H. and Conko, G. *The Protocol’s Illusionary Principle*, *Nature Biotechnology*, 2000, 18, 360-61, and Miller, H.I. and G. Conko. *The Perils of Precaution: Why Regulators’ “Precautionary Principle” Is Doing More Harm Than Good*, *Policy Review*, June-July 2001, 25-39.

power station, the introduction of a new drug into the pharmacy, or the consumption of food from gene-spliced plants, the precautionary principle overemphasizes the potential for technologies to pose unique, extreme, or unmanageable risks. What is missing from precautionary calculus is an acknowledgment that even when technologies introduce new risks, very often they confer net benefits – that is, their use reduces many other, far more serious and costly hazards. Examples include blood transfusions, MRI scans, and automobile seat belts and air bags, all of which offer immense benefits and only minimal risk.

Unnecessary delay in granting marketing approval for these and other technologies denies consumers access to products that could substantially reduce the risk of injury, or even death; this is a common side effect of the application of the precautionary principle. Thus, the use of the precautionary principle often distorts the risk equation, heightens risk, and actually causes harm to public health and the environment. The oversight of recombinant DNA technology used for agriculture and food production offers a vivid example of how the precautionary principle can systematically weaken science, technology, public health, the environment, and innovation.

This paper first describes the general scientific consensus regarding the risks associated with recombinant DNA-modified, or gene-spliced, organisms and the implications of that consensus for the regulation of organisms in the field, and of food in the marketplace. Next, the paper examines the potential for poorly conceived regulation actually to increase risk, paying particular attention to the potentially risk-enhancing danger of existing precautionary regulatory policies. It concludes with a discussion of scientifically defensible, risk-based frameworks for the regulation of products that involve the use of recombinant DNA technology.

SCIENCE AND THE RISKS OF RECOMBINANT DNA TECHNOLOGY

The creation of the first recombinant DNA-modified organism in 1973 marked the advent of

a promising new technique for the development of new medical, agricultural, environmental, and industrial products. Soon afterward, scientists and policymakers began to consider possible approaches to the oversight of the testing and use of recombinant DNA-modified organisms and products derived from them. During the last 25 years, dozens of scientific bodies, including the U.S. National Academy of Sciences,³²³ the American Medical Association,³²⁴ the Institute of Food Technologists,³²⁵ and the United Nations' Food and Agriculture Organization and World Health Organization³²⁶ have analyzed the oversight that is appropriate for gene-spliced organisms and arrived at remarkably congruent conclusions:

- The newer molecular techniques for genetic improvement are an extension, or refinement, of earlier, far less precise ones;
- Adding genes to plants or microorganisms does not necessarily make them less safe either to the environment or to eat;
- The risks associated with gene-spliced organisms are the same in kind as those associated with conventionally modified organisms and unmodified ones; and
- Regulation should be based upon the risk-related characteristics of individual products, regardless of the techniques used in their development.

An authoritative 1989 analysis of the modern gene-splicing techniques published by the NAS's research arm, the National Research Council, concluded that "the same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and

³²³ NAS, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*, Washington, DC: Council of the U.S. Academy of Sciences/National Academy Press, 1987.

³²⁴ AMA, *Report 10 of the Council on Scientific Affairs (I-00): Genetically Modified Crops and Foods*, Chicago, IL: American Medical Association, 2000, available at: <http://www.ama-assn.org/ama/pub/article/2036-3604.html>.

³²⁵ IFT, *IFT Expert Report on Biotechnology and Foods*, Chicago, IL: Institute of Food Technologists, 2000.

³²⁶ WHO, *Strategies for Assessing the Safety of Foods Produced by Biotechnology: Report of a Joint FAO/WHO Consultation*, Geneva, Switzerland: World Health Organization, 1991.

those produced by classical methods,” but it went further, observing that gene-splicing is more precise, circumscribed, and predictable than other techniques:

“Recombinant DNA methodology makes it possible to introduce pieces of DNA, consisting of either single or multiple genes, that can be defined in function and even in nucleotide sequence. With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise number or the traits that have been transferred is difficult, and we cannot always predict the [characteristics] that will result. With organisms modified by molecular methods, we are in a better, if not perfect, position to predict the [characteristics].”³²⁷

The same principles were emphasized in the comprehensive report by the United States National Biotechnology Policy Board, which was established by the Congress and comprised of representatives from the public and private sectors. The report concluded:

“[t]he risks associated with biotechnology are not unique, and tend to be associated with particular products and their applications, not with the production process or the technology per se. In fact biotechnology processes tend to reduce risks because they are more precise and predictable. The health and environmental risks of not pursuing biotechnology-based solutions to the nation’s problems are likely to be greater than the risks of going forward.”³²⁸

An analysis of food safety published in 2000 by the Institute of Food Technologists addressed regulatory approaches to gene-spliced foods and specifically took current regulatory policies to task. The report concludes that the evaluation of gene-spliced food “does not require a fundamental change

in established principles of food safety; nor does it require a different standard of safety, even though, in fact, more information and a higher standard of safety are being required.” It went on to state unequivocally that theoretical considerations and empirical data do “not support more stringent safety standards than those that apply to conventional foods.”³²⁹

Yet, despite the broad consensus of the scientific community about the essential similarities of old and new methods for genetic improvement, and the importance of the new techniques to science and commerce, only recombinant DNA-modified organisms are, as a class, subjected to lengthy, mandatory premarket regulatory review. For gene-spliced plants, both the fact and degree of regulation are determined by the production methods – that is, the use of gene-splicing techniques, per se, triggers extraordinary premarket testing requirements for human health and environmental safety, regardless of the level of risk posed.

Dozens of new plant varieties produced through hybridization and other traditional methods of genetic improvement enter the marketplace and food supply each year without any scientific review or special labeling. Many such products are from “wide cross” hybridizations in which large numbers of genes – including even entire chromosomes or whole genomes – are moved from one species or one genus to another, and incorporated randomly into the host genome, yielding a plant variety that does not and cannot exist in nature. Some “wide crosses” can be produced through ordinary sexual reproduction. Others are the result of in vitro techniques of protoplast fusion and embryo rescue, which overcome physical or genetic barriers to the development of fertile progeny. Many varieties of plants derived from wide crosses – which under any reasonable definition may be said to be “genetically engineered” or “genetically modified” – are consumed widely and routinely in the United States, Europe, and elsewhere; they include wheat, corn, rice, oat, tomato, potato, rice, pumpkin, and black currant. As discussed in chapter two, still other novel plant varieties are produced with somaclonal variation techniques or

³²⁷ NRC, *Field Testing Genetically Modified Organisms: Framework for Decisions*, U.S. National Research Council/National Academy Press Washington, D.C., 1989.

³²⁸ *National Biotechnology Policy Board Report* National, Institutes of Health, Office of the Director, Bethesda, MD, 1992.

³²⁹ IFT, 2000.

by treating plant cells with radiation or chemicals to produce random genetic changes that give rise to new traits.

Although all of these breeding techniques have the potential to create unexpected agronomic, environmental, or health effects, in most cases the products of the relatively imprecise “traditional” methods of genetic modification are subject to no governmental premarket regulation whatever. Consider, for example, the relatively new manmade “species” *Triticum agropyrotriticum*, which resulted from the combination of genes from bread wheat and a grass sometimes called quackgrass or couch grass. Possessing all the chromosomes of wheat and one extra whole genome from the quackgrass, *T. agropyrotriticum* has been independently produced in the former Soviet Union, Canada, the United States, France, Germany, and China. It is grown for both animal feed and human food. At least in theory, several kinds of problems could result from such a genetic construction that introduces tens of thousands of foreign genes into an established plant variety. These include the potential for increased invasiveness of the plant in the field, and the possibility that quackgrass-derived proteins could be toxic or allergenic. But regulators have evinced no concern about these possibilities, and these plant varieties, which are certainly “genetically modified,” are not subject to review.

Another striking example of the inconsistency of government regulatory policy involves induced-mutation breeding, which has been in common use since the 1950s. The ionizing radiation and toxic chemicals used to induce random genetic mutations most often kill the plants (or seeds) or cause detrimental genetic changes. But on rare occasions, the result is a desirable mutation – for example, one producing a new trait in the plant that is agronomically useful, such as altered height, more seeds, or larger fruit. In these cases, breeders have no detailed knowledge of the nature of the genetic mutation(s) that produced the useful trait, or of what other mutations might have occurred in the plant.³³⁰ Yet the approximately 2,250 mutation-bred plant varieties from a range of different species that have been marketed over the last half century have been subject to no

formal premarket regulation whatever, although several – including two varieties of squash and one each of potato and celery – were found to have dangerous levels of endogenous toxins and were banned from commerce.

Why are novel genetic constructions crafted with these older techniques exempt from regulation from the dirt to the dinner plate, from the turf to the tongue? Why don't regulatory regimes require new genetic variants made with older techniques to be evaluated for increased weediness or invasiveness, and for new allergens or toxins that could show up in food? The answer is based on millennia of experience with genetically improved (but pre-gene-splicing) crop plants: even the use of relatively crude and unpredictable genetic techniques for the improvement of crops and microorganisms poses minimal – but, as noted above, not zero – risk to human health and the environment. Plant breeders routinely use a number of well-established practices to identify and eliminate plants that exhibit unexpected adverse traits prior to commercial use, and there is widespread consensus that regulation need be no more stringent than post-marketing surveillance for any problems. And, echoing the quotations above from the 1989 National Research Council study, scientists agree that the same practices are appropriate and sufficient to ensure the safety of plants developed with recombinant DNA techniques.

Paradoxically, only the more precisely crafted, gene-spliced crops are exhaustively, repeatedly (and expensively) reviewed before they can enter the field or food supply. Throughout most of the world, gene-spliced crop plants, such as herbicide-tolerant soy and canola, and insect-resistant corn and cotton, are subject to lengthy, hugely expensive mandatory testing and premarket evaluation, while plants with similar properties but developed with older, less precise genetic techniques are exempt from such requirements. In the *T. agropyrotriticum* example above, the wheat variety containing tens of thousands

³³⁰ IAEA, *Officially Released Mutant Varieties: The FAO/IAEA Database*, Vienna, Austria: Joint FAO-IAEA Division, International Atomic Energy Agency, December 2000.

of newly introduced genes from a wild plant species not previously found within the food supply is subject to no governmental strictures or review at all when it is field tested or, ultimately, enters the food chain. However, if a single gene from couchgrass (or any other organism) were introduced into wheat by means of recombinant DNA techniques, the resulting variety would be subject to extraordinary, hugely expensive, redundant regulatory regimes.

This inconsistent approach to the introduction of new plant varieties violates both a fundamental principle of regulation – that the degree of regulatory scrutiny should be commensurate with risk– and the legal dictum that similar situations should be treated in similar ways. It is contradicted by common sense, in that regulators have adopted an approach in which there is *inverse* proportionality between risk and the degree of scrutiny. Only the more precisely crafted and more predictable gene-spliced organisms are subjected to extensive and expensive testing and monitoring (and in some places, labeling) regimes. No traditional food derived from a “conventionally modified” plant variety could pass such testing regimes, in the field or prior to entering the food supply.

What does this regulatory inconsistency mean in practice? If a student doing a school biology project takes a packet of “conventional” tomato or pea seeds to be irradiated at the local hospital x-ray suite and plants them in his backyard in order to investigate interesting mutants, he need not seek approval from any local, national, or international authority. However, if the seeds have been modified by the addition of one or a few genes via gene-splicing techniques – even if the genetic change is merely to remove a gene – this would-be Mendel faces a mountain of bureaucratic paperwork and expense (to say nothing of the very real possibility of vandalism by anti-technology activists, because the site of the experiment must be publicized). The same applies, of course, to professional agricultural scientists in industry or academia.

In the United States, the Department of Agriculture requirements for paperwork and field trial design make field trials with gene-spliced

organisms 10 to 20 times more expensive than the same experiments with virtually identical organisms that have been modified with conventional genetic techniques.³³¹ By EPA’s own radically conservative estimates, the regulatory costs of its Plant-Incorporated Protectants regulation will raise the average expense per “permit submission” for testing a new plant from \$200,000 to \$500,000 – a 150 percent increase, only because the field trials employ a more precisely constructed and more predictable plant variety! Don Gordon, President of the Agricultural Council of California, has predicted that the EPA’s regulatory approach will have profound impacts on companies’ ability to perform R&D: “...research and development of ‘plant pesticides’ will continue; but, only a few very large companies will have the resources necessary to cope with this new and costly bureaucratic process.”³³²

Agricultural economists have studied the spectrum of indirect, non-regulatory costs of segregation and identity preservation that are required when regulatory policies focus on recombinant DNA technology. Richard Maltzbarger and Nicholas Kalaitzandonakes at the University of Missouri-Columbia, for example, analyzed several case studies of segregation of high-oil corn and concluded that the sum of “coordination, segregation and opportunity costs” is in the range of 16 to 27 cents per bushel, an amount that is significant.³³³ Moreover, they note that the analyses were developed assuming a five percent allowable threshold of contamination from other varieties or hybrids, and that costs would be much higher if lower thresholds were mandated.

These kinds of regulation-related burdens will disproportionately affect California, which “has a heavy burden of existing and emerging plant pests,

³³¹ Miller, Henry I., *Policy Controversy in Biotechnology: An Insider’s View*, R.G. Landes Company, Austin, TX, 1997.

³³² Seibert, Jerry, *Regressive EPA Policy: Guest Opinion*, California Farmer, June 1997.

³³³ Maltzbarger, Richard and N Kalaitzandonakes Study reveals hidden costs in IP supply chain, 2000, http://www.biotech-info.net/hidden_costs2.html, accessed 17 February 2001.

as well as the most diverse agricultural production system in the nation – involving more than 250 mainly minor-use-pesticide crops.³³⁴

Although the handful of large agribusiness companies involved in agricultural biotechnology have actually benefited from such extensive and expensive regulatory regimes (*vide infra*) – buying up small competitors unable to endure inflated regulatory costs – academic researchers, the ultimate engine for innovation, have been among the most severely affected victims of excessive, ill-conceived regulation. Operating on small budgets, their ability to perform field trials of recombinant plants and microorganisms has been markedly restricted.

Some regulators remonstrate that such rules constitute a scientifically defensible regulatory algorithm that does indeed focus on such risk-related characteristics as weediness, pathogenicity, toxicity, and potential for outcrossing. And many of these rules might seem reasonable if considered narrowly – that is, if one ignores the flawed scope of what is encompassed by the oversight regime. But that scope – the inclusion of gene-spliced plants while excluding all others – is so flawed and inappropriate that it invalidates the approach.

Another similar example of an inappropriate choice of the scope of oversight invalidating an approach to regulation is the United Nations' recent attempt to ensure that potentially allergenic gene-spliced foods will be detected before consumers can be exposed to them. One of the theoretical concerns that have been raised about foods derived from gene-spliced plants is that consumers might experience allergic reactions to novel proteins, or to known allergens in an unexpected milieu (such as if a gene coding for a peanut protein were transferred to a potato). A panel of consultants to the United Nations' Food and Agriculture Organization and World Health Organization has proposed a protocol for the testing of such foods.³³⁵ Intended to guide testing in order to determine the allergenic potential of gene-spliced foods, it poses questions – such as, is the source of the

introduced gene allergenic, and does the gene product resemble known allergens – in a neat little flow chart.

Considered in a vacuum, it may seem to be a reasonable approach; the questions are scientific, after all, and the algorithm has a certain logic. However, it ignores the realities of the development and commercialization of new plant varieties, and the way that foods derived from them traditionally are regulated – or to be more precise, the way that they are *unregulated*. Consider the example of *Triticum agropyrotriticum* described above, in which a new manmade “species” was created by combining all the genes from both bread wheat and a wild grass species known as quackgrass.

Conceivably, such a genetic construction that introduces tens of thousands of foreign genes more or less at random into an established plant variety could pose a serious risk that novel proteins could be toxic or allergenic. But regulators have never shown concern about these risk-related issues, nor would new plants created in this way be subject to this new FAO/WHO proposal. Thus, although it might enjoy a patina of scientific respectability, the FAO/WHO allergenicity protocol is compromised by adopting a scope that simply makes no scientific sense. When asked why the consultants didn't remedy the inappropriate choice of scope, one of the experts on the panel responded candidly that although they were, of course, aware of the flaws, they were specifically directed by UN administrators not to address them.

If those crafting regulatory approaches to novel plant varieties were genuinely interested in reducing risk, surely greater precaution would be appropriate not to gene-splicing but to the cruder, less precise, less predictable “conventional” forms of genetic modification. Instead, regulators have chosen to set the burden of proof far higher for gene-splicing technology than for conventional plant breeding. This regulatory approach is inconsistent with the scientific consensus about the risks associated with gene-spliced organisms, and it misallocates regulators' resources. A more scientifically defensible, rational approach is necessary if regulators are to achieve the dual goals of reducing overall product risk and efficiently allocating public resources.

³³⁴ Seibert, 1997.

³³⁵ FAO, *Evaluation of Allergenicity of Genetically Modified Foods: Report of a /WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology*, Food and Agriculture Organization, Rome, Italy, January 2001.

THE DANGER OF PRECAUTION

All technologies pose potential risk. In order to reduce net risks most effectively, the degree of regulatory scrutiny applied to individual products should be commensurate with the degree and type of risk being addressed. For example, different innovations in automobile design can (and should) elicit highly disparate regulatory responses: the new electric/internal combustion engine hybrid cars can be regulated in much the same way as conventional vehicles, but a nuclear-powered car with a plutonium-containing reactor would need to be approached quite differently.

The fundamental flaw in precautionary-style regulation is that it too narrowly focuses on the risk of innovation, while ignoring the impact of the *absence* of innovation. This distorted approach to risk distracts consumers and policymakers from many known, significant threats to human health and diverts limited public health resources from those genuine and far greater risks. Consider, for example, the environmental movement's misguided crusade to rid society of all chlorinated compounds.

By the late 1980s, environmental activists were attempting to convince water authorities around the world of the possibility that carcinogenic byproducts from chlorination of drinking water posed a potential cancer risk. Peruvian officials, caught in a budget crisis, used this supposed threat to public health as a justification to stop chlorinating much of their country's drinking water. That decision contributed to the acceleration and spread of Latin America's cholera epidemic, which afflicted more than 1.3 million people and killed at least 11,000 between 1991 and 1996.³³⁶

Activists have since extended their anti-chlorine campaign to so-called "endocrine disrupters," or "endocrine modulators," asserting that certain manmade chemicals mimic or interfere with human hormones (especially estrogens) in the body and thereby cause a range of abnormalities and diseases related to the endocrine system.

It is well documented that the demonstration that a chemical administered at high doses causes cancer in certain laboratory animals does not prove that it can cause cancer in humans under normal circumstances – both because of different susceptibilities and because humans are ordinarily subjected to far lower exposures to synthetic environmental chemicals. The American Council on Science and Health and others have explored the endocrine disrupter hypothesis and found that, while high doses of certain environmental contaminants produce toxic effects in laboratory test animals – in some cases involving the endocrine system – humans' actual exposure to these suspected endocrine modulators is many orders of magnitude lower. No consistent, convincing association has been demonstrated between real-world exposures to synthetic chemicals in the environment and increased cancer in hormonally sensitive human tissues.³³⁷

Moreover, humans are routinely exposed through their diet to many estrogenic substances (substances that have an effect similar to that of the human hormone estrogen) found in many plants. Dietary exposures to these plant estrogens, or phytoestrogens, are far greater than exposures to supposed synthetic endocrine modulators, and no adverse health effects have been associated with the overwhelming majority of these dietary exposures.

Furthermore, there is currently a trend toward lower concentrations of many contaminants in air, water, and soil – including several that are suspected of being endocrine disrupters. Some of the key research findings that stimulated the endocrine disrupter hypothesis originally have been retracted or are not reproducible. The available human epidemiological data show no consistent, convincing evidence of negative health effects related to industrial chemicals that are suspected of disrupting endocrine systems. In spite of that, activists and many government regulators continue to invoke the need for precautionary

³³⁶ Anderson, Christopher, "Cholera epidemic traced to risk miscalculation," *Nature*, Vol.354, November 28, 1991, p. 255.

³³⁷ ACSH, *Endocrine Disruptors: A Scientific Perspective*, American Council on Science and Health New York, NY, July 1999.

(over-) regulation, and even outright bans, of various products.

Anti-chlorine campaigners more recently have turned their attacks to phthalates, liquid organic compounds added to certain plastics to make them softer. These soft plastics are used for important medical devices, particularly fluid containers, blood bags, tubing and gloves; children's toys such as teething rings and rattlers; and household and industrial items such as wire coating and flooring. Again invoking the precautionary principle, activists claim that phthalates might have numerous adverse health effects – even in the face of significant scientific evidence to the contrary. Some governments have taken these unsupported claims seriously, and several formal and informal bans have been implemented around the world. Whole industries have been terrorized, consumers denied product choices, and doctors and their patients deprived of lifesaving tools.

Biased Decision Making

The European Union is a prominent advocate and practitioner of the precautionary principle, particularly with respect to gene-splicing, incorporating it explicitly into various regulations, standards, and agreements. In the United States, where the precautionary principle is thought of (if it is thought of at all) as a concept advocated by the radical environmental movement and used by national regulators as political cover for trade barriers, regulatory agencies have not incorporated that precise term of art into law or official policies. That does not prevent many U.S. regulatory agencies from commonly practicing excessively precautionary regulation, however, and the regulation of such products as pharmaceuticals, food additives, synthetic pesticides and other chemicals, and gene-spliced plants and microorganisms, is without question “precautionary” in nature. The primary distinctions between precautionary regulation in the United States and the use of the precautionary principle in Europe are degree, areas of application (reflecting diverse prejudices about certain products, technologies, and activities), and semantics.

The precautionary principle can distort the process of selecting a regulatory approach for

a new technology or product by amplifying a systematic bias that exists normally in regulatory decision making. Regulators routinely face an intrinsically asymmetrical incentive structure in which they are compelled to address the potential harms from new activities or products, but are free to discount the hidden risk-reducing properties of unused or under-used ones. The result is a lopsided decision-making process that is inherently biased against change and therefore against innovation.

This asymmetry arises from the fact that there are two basic kinds of mistaken decisions that a regulator can make. First, a harmful product can be approved for marketing – called a Type I error in the parlance of risk analysis. Second, a product potentially beneficial to society may be rejected or delayed, can fail to achieve marketing approval at all, or may be inappropriately withdrawn from the market – a Type II error. In other words, a regulator commits a Type I error by permitting something harmful to happen, and a Type II error by preventing something salutary from becoming available. Both situations have negative consequences for the public, but the outcomes for the regulator are very different.

Examples of this Type I-Type II error dichotomy abound in both the U.S. and Europe, but it is perhaps illustrated most clearly in FDA's new drug approval process. A classic illustration is the FDA's approval in 1976 of the swine flu vaccine – generally perceived as a Type I error because, although the vaccine was effective at preventing influenza, it had a major side effect that was unknown at the time of approval. A small number of patients suffered temporary paralysis from Guillain-Barré Syndrome. This kind of mistake is highly visible and has immediate consequences: regulators are the focus of criticism from the media, self-styled public-interest groups, and the Congress. Because regulatory officials' careers might be damaged irreparably by the good-faith but mistaken approval of a high-profile product, their decisions are often made defensively – in other words, to avoid Type I errors at any cost.

Former FDA Commissioner Alexander Schmidt aptly described the regulator's plight:

“In all our FDA history, we are unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of a new drug have been so frequent that we have not been able to count them. The message to FDA staff could not be clearer. Whenever a controversy of a new drug is resolved by approval of the drug, the agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made. The Congressional pressure for negative action is, therefore, intense. And it seems to be ever increasing.”³³⁸

Type II errors in the form of excessive governmental requirements and unreasonable decisions can cause a new product to be “disapproved,” in Schmidt’s phrase, or the approval to be delayed. Unpredictable, arbitrary delays in getting products to market are a source of “financial risk,” and are, therefore, anathema to innovators. These delays discourage research and development, lessen competition, inflate the ultimate price of the product, and diminish the number of products that get to market.

Consider, for example, the FDA’s precipitate response to the 1999 death of a patient in a University of Pennsylvania gene therapy trial for a genetic disease. The cause of the incident had not been identified and the product class (a preparation of the needed gene, encased in a viral delivery system, that would be administered to the patient) had been used in a large number of patients with no fatalities and serious side effects in only a few percent of patients. Nevertheless, apparently wanting to be perceived as reacting vigorously to a Type I error, regulators halted not only the trial in which the fatality occurred, but all the other gene-therapy studies at the same university, and similar studies at other universities and in industry. By these actions, by publicly excoriating and humiliating the researchers involved, and by imposing new reporting and monitoring

requirements on all gene therapy investigations, the FDA has dampened enthusiasm for the entire field of gene therapy, among both investigators and venture capitalists.

Although Type II errors can dramatically compromise public health, they seldom gain public attention. Often, only the employees of the company that makes the product and a few stock market analysts and investors are knowledgeable about unnecessary delays. And if the regulator’s excessive risk-aversion precipitates a corporate decision to abandon the product, cause and effect are seldom connected in the public mind. Naturally, the companies themselves are loath to complain publicly about a mistaken FDA judgment because the agency has so much discretionary control over their ability to test and market products. As a consequence, there maybe no direct evidence of, or publicity about, the lost societal benefits and the culpability of regulatory officials.

Exceptions exist, of course. A few activists, such as the well-organized AIDS advocacy groups that closely monitor the FDA, scrutinize agency review of certain products and aggressively publicize Type II errors. Congressional oversight should provide another critical check on regulators’ performance, but as noted above by former FDA Commissioner Schmidt, only rarely does it focus on Type II errors. Type I errors make for better Capitol Hill theater, after all, with patients who have been injured, and their family members, prominently featured. And even when such mistakes are exposed, regulators frequently defend Type II errors as erring on the side of caution – in effect, invoking the precautionary principle – as they did in the wake of the University of Pennsylvania gene therapy case. Legislators, the media, and the public too often accept this euphemism uncritically, and our system of pharmaceutical oversight becomes progressively less responsive to the public interest.

The FDA is not unique in this regard, of course. All regulatory agencies are subject to the same sorts of social and political tensions that cause them to be castigated when hazardous products make it to market (even if those products produce net benefits), but to escape blame when they

³³⁸ Schmidt, Alexander, Testimony before the Senate Labor and Human Resources Committee, 1974.

keep beneficial products from being available to consumers. Adding the precautionary principle's bias against new products into the public policy mix further encourages regulators to make Type II errors in their eagerness to avoid Type I errors.

For regulators of gene-spliced plants, assessing the risk portion of the risk-benefit calculation is easy, because both theory and empirical evidence indicate that the risks of the techniques, per se, are negligible. What one is left with, then, is essentially the intrinsic risk of the host plant – with which there is generally considerable experience – taking into consideration any newly added traits. But leaving aside the risk, the benefit – or, alternatively, the risk-reducing – portion of the calculation has seemingly been ignored, as noted above a common failure of precautionary regulation. For example, some of the most successful of the gene-spliced crops, especially cotton and corn, have been constructed by splicing in a bacterial gene that produces a protein toxic to predatory insects, but not to people or other mammals. Not only do these gene-spliced corn varieties repel pests, but grain obtained from them is less likely to contain *Fusarium*, a toxic fungus often carried into the plants by the insects. That, in turn, significantly reduces the levels of the fungal toxin fumonisin, which is known to cause fatal diseases in horses and swine that eat infected corn, and esophageal cancer in humans. When harvested, these gene-spliced varieties of grain also end up with lower concentrations of insect parts than conventional varieties. Thus, gene-spliced corn is not only cheaper to produce, but is more esthetically acceptable and a potential boon to public health. Moreover, by reducing the need for spraying chemical pesticides on crops, it is environmentally and occupationally friendly.

Other products offer agronomic, nutritional and environmental advantages. Gene-spliced herbicide-resistant crops have permitted farmers to adopt more environment-friendly no-till farming practices. Crops now in development with improved yields would allow more food to be grown with less water and on less acreage, conserving more land area for wildlife or other uses. Genes have been isolated that enable plants to resist soil salinization, which lowers yields, and to hyperaccumulate heavy metals when grown in toxic waste sites. Recently developed

plant varieties with enhanced vitamins, minerals, and dietary proteins can dramatically improve the health of hundreds of millions of the malnourished populations of less developed countries.

These are the kinds of tangible environmental and health benefits that invariably are given little or no weight in precautionary risk calculations. But it should be emphasized that, even in the absence of such monumental benefits, both potential and current, regulators' estimation of risk in the risk/benefit calculation is far from what scientific consensus would dictate.

Wealthier Is Healthier

In addition to the direct negative societal impacts caused by the loss of beneficial products, government over-regulation implemented in the name of the precautionary principle poses some indirect and subtle perils. Money spent on implementing and complying with regulation (justified or not) exerts an "income effect" that reflects the correlation between wealth and health, an issue popularized by the late political scientist Aaron Wildavsky. It is no coincidence, he argued, that richer societies have lower mortality rates than poorer ones.

Wealthier individuals are able to purchase better health care, enjoy more nutritious diets, and lead generally less stressful lives. Conversely, the deprivation of income itself has adverse health effects, including an increased incidence of stress-related problems, including ulcers, hypertension, heart attacks, depression, and suicides. To deprive communities of wealth, therefore, is to enhance their risks.

It is difficult to quantify precisely the relationship between the deprivation of income and mortality, but academic studies suggest, as a conservative estimate, that every \$7.25 million of regulatory costs will induce one additional fatality through this "income effect."³³⁹ The excess costs in the tens of billions of dollars required annually by precautionary regulation for various classes of consumer products would, therefore, be expected to cause thousands of deaths per year. Arguably,

³³⁹ Keeney R.L., "Mortality risks induced by economic expenditures," *Risk Analysis*, 2000, 147:148. See also Catalano R. "The Health Effects of Economic Insecurity," *American Journal of Public Health*, 1991; 81:1148.

all the regulations and policies, the new boxes on the organization charts, boards and panels, data bases, websites, newsletters, studies and reports (including this one) that impose costs on the public and private sector all exert this income effect. These are the real costs of “erring on the side of safety,” which amount to what John Graham, the head of the regulatory office in the Bush administration’s Office of Management and Budget, has referred to as “statistical murder.” The expression “regulatory overkill,” thus, may not be not empty rhetoric.

Instead of precautionary regulation, Wildavsky advocates a strategy of “resilience,” in which society accumulates knowledge about risks in a process of trial and error. Research, development, and marketing of new products should be encouraged, and regulators permitted to restrict such activities only upon a showing of bona fide evidence of potential harm, not mere speculation or pseudo-controversy generated by vocal activists. Such a strategy allows society to take maximum advantage of the risk-reducing benefits of new technologies, while building the resources necessary to cope with the inevitable harms that result both from the unanticipated risks of new products and from the risks posed by the absence of beneficial technologies. In other words, risk-taking, not risk avoidance, improves overall safety and health.³⁴⁰

LEGAL UNCERTAINTY

During the last few years, skeptics have begun more vigorously to question the theory and practice of the precautionary principle. In response to those challenges, the European Commission (EC), a prominent user and abuser of the precautionary principle, in 2000 published a formal communication to clarify and to promote the legitimacy of the concept. The EC

resolved that, under its auspices, precautionary restrictions would be “proportional to the chosen level of protection,” “nondiscriminatory in their application,” and “consistent with other similar measures.” The Commission also avowed that EC decision makers would carefully weigh “potential benefits and costs.”³⁴¹ The Commission’s Health Commissioner, David Byrne, repeated all of these points in an article on food and agriculture regulation in the journal *European Affairs*. In it, he asked rhetorically, “How could a Commissioner for Health and Consumer Protection reject or ignore well founded, independent scientific advice in relation to food safety?”³⁴²

Byrne himself should be able to tell us: the ongoing dispute between his European Commission and the United States and Canada over restrictions on hormone-treated beef cattle is exactly such a case. The EC argued that the precautionary principle permits restriction of imports of U.S. and Canadian beef from cattle treated with certain growth hormones. A scientific committee assembled by the WTO dispute resolution panel found that even the scientific studies cited by the EC in its own defense did not indicate a safety risk when the hormones in question were used in accordance with accepted animal husbandry practices.³⁴³ Thus, the WTO ruled in favor of the U.S. and Canada because the scientific evidence clearly favored their position. Nevertheless, the EC continues to enforce restrictions on hormone-treated beef, a blatantly unscientific policy that belies the Commission’s protestations that the precautionary principle will not be abused.

The European Commission and individual countries of Europe have long applied the precautionary principle to the regulation of the products of recombinant DNA technology, or gene-splicing. By the early 1990s, many of the countries in Western Europe, as well as the EC itself, had

³⁴⁰ Wildavsky, “Public Policy,” Chapter 6 in Bernard D. Davis, Ed. *The Genetic Revolution: Scientific Prospects and Public Perceptions*, The Johns Hopkins University Press, Baltimore, MD, 1991, pp. 77-104.

³⁴¹ EC, *Communication from the Commission on the Precautionary Principle*, COM, 2000, Commission of the European Communities, Brussels, Belgium, February 2, 2001.

³⁴² Byrne, David, “Food Safety: Continuous Transatlantic Dialogue is Necessary,” *European Affairs*, Vol. 1, No. 2, Spring 2000, pp. 80-85.

³⁴³ WTO, *EC Measures Concerning Meat and Meat Products (Hormones): Report of the Appellate Body*, World Trade Organization, Geneva, Switzerland, January 16, 1998.

erected unscientific and unnecessarily strict rules regarding the testing and commercialization of gene-spliced crop plants. In 1999, the Commission explicitly invoked the precautionary principle in establishing a moratorium on the approval of all new gene-spliced crop varieties, pending approval of an even more strict EU-wide regulation.

Notwithstanding the EC's promises that the precautionary principle would not be abused, all of the stipulations enumerated by the Commission have been ignored or reinterpreted in its regulatory approach to gene-spliced (or in their argot, "genetically modified" or "GM") foods. Rules for gene-spliced plants and microorganisms are inconsistent, discriminatory, and bear no proportionality to risk.

The European Commission's abuses demonstrate that clarifications and promises are of little use in the absence of an enforceable commitment to act in a rational, responsible way. Remarkably, although the European Commission characterized its 2000 communication on the precautionary principle as an attempt to impart greater consistency and clarity, it specifically declined to define the principle, adding naively, "it would be wrong to conclude that the absence of a definition has to lead to legal uncertainty." Although reliance on regulatory agencies and courts to define an elaborate statutory policy is not unusual, this failure to define what purports to be a fundamental principle makes confusion inevitable; it leaves innovators' legal rights and regulators' legal obligations hostage to the subjective judgment of governments or individual regulators (or, perhaps, even trade officials or other politicians).

As it is being applied, the precautionary principle seldom provides either evidentiary standards for "safety" or procedural criteria for obtaining regulatory approval, no matter how much evidence has been accumulated. In effect, regulators are given *carte blanche* to decide what is "unsafe" and what is "safe enough," with no means to ensure that their decisions actually reduce overall risk or that they make any sense at all. The precautionary principle tends to make governments less accountable because its lack

of definition allows regulators to justify any decision.

Ultimately, such legal uncertainty poses very real societal costs. Not only are consumers denied the opportunity to use beneficial new products, but the high cost of arbitrary and lengthy regulatory reviews can discourage smaller companies and academic researchers from proceeding with products that are expected to be of marginal profitability (or that "merely" offer the possibility of information of purely scientific information). Furthermore, the cost of excess regulation also will be reflected in the market prices of those products that do eventually make it to market. In effect, ill-conceived regulation imposes upon them a punitive tax. And in the case of recombinant DNA technology and gene-spliced plants, this penalty can be quite substantial.

Finally, as pointed out by law professor Drew L. Kershen,³⁴⁴ another completely different kind of risk must be considered: potential legal liability to food-producing companies that attempt to make their products "gene-splicing-free." In response to some of the various pseudo-controversies that have engulfed gene-spliced crops and foods, many food companies have considered avoiding gene-spliced crops altogether in their feed or food supplies, and several have actually done so. Kershen cites the example of Gerber, which in 1999 announced that its baby food products would no longer contain any gene-spliced ingredients, and that it would attempt to shift to organic crops that are grown without synthetic pesticides or fertilizers. However, these crops generally contain higher levels of mycotoxins, which cause illness and death in animals and cancer in humans, than either conventional or gene-spliced crops. Kershen argues that such a strategy, therefore, creates the potential for claims of liability from damage (cancer) by consumers. Under a claim of strict products liability, Kershen says they could allege a manufacturing defect based on contamination in the baby food, and also a design defect, "because Gerber knew of a baby food designed (made) with

³⁴⁴ Kershen, Drew L., *Genetic Enhancements Can Reduce Food Company Legal Risks. Legal Background*, Washington Legal Foundation, Washington, DC, September 7, 2001.

less risky ingredients [but] purposefully chose to use the riskier design – i.e. Gerber chose to use non-GMO ingredients knowing that these have a higher risk of mycotoxin contamination.”

Kershen cites violation of environmental regulations as another legal risk to food producers who choose systematically to reject gene-spliced crops. He describes that, under pressure from fast-food companies such as McDonald’s and Wendy’s, potato grower J.R. Simplot and potato processors have imposed requirements on farmers not to use any gene-spliced plants, and that by doing so, potato processors “are putting themselves at legal risk of being held accountable for their growers’ environmental [non-] compliance.” This risk arises from the fact that through “technology-forcing” regulations, the EPA often intentionally imposes over-stringent regulatory standards for pesticides, on the theory that companies will be forced to invest in research and development that will provide innovative ways to meet the standard. Thus, potato growers who have difficulty meeting these standards could “argue to the EPA that their potato processors have contractually forced them to use more pesticides than necessary by requiring non-GMO varieties of potatoes,” instead of EPA-approved gene-spliced crops that do not require chemical pesticides.

ALTERNATIVES TO “PRECAUTIONARY” REGULATION

As discussed above, precautionary-style regulation fails to protect public health or the environment because it over-emphasizes the risks of the testing and use of new processes and products, while it ignores possible net reductions of risk; thereby, it diverts attention and resources from potentially greater harms that may result from forgoing beneficial new technologies. In order to more effectively reduce the overall risks of agricultural practices and to enhance food safety, the regulation of new plant varieties should focus on, and be triggered by, the risk-related characteristics of new products, not on the techniques used in creating them. Below, we discuss an approach to regulation that is, in contrast to the precautionary principle, scientifically defensible and risk-based, that links

the degree of oversight with the degree of risk, and that is sufficiently flexible to be adaptable to various views of regulation.

PLANTS IN THE FIELD

Several years ago, the Stanford Project on Regulation of Agricultural Introductions developed a widely applicable regulatory model for the field testing of any organism, whatever the method(s) employed in its construction. By enabling accurate, scientific determinations of the risks posed by the introduction of any type of organism into the field, this regulatory model enables governments to promote enhanced agricultural productivity and innovation, while protecting valuable ecosystems. It offers regulatory bodies a highly adaptable, scientific method for field-testing potential agricultural crops or other organisms. The approach is widely applicable whether the introduced organisms are “naturally” occurring, non-indigenous “exotics,” or have been genetically improved by either old or new techniques. It offers an easily adaptable route to comprehensive, cost-effective regulation, thereby benefiting academic and industrial researchers, as well as government regulators.

In January 1997, the project assembled a group of approximately 20 agricultural scientists from five nations at a workshop held at the International Rice Research Institute (IRRI), Los Baños, Philippines.³⁴⁵ The purpose of the IRRI Conference was to seek consensus on a broad, science-based approach that would evaluate all biological introductions, not just the introduction of gene-spliced organisms. There was already abundant evidence that severe ecological risks can be associated with “exotics,” or, in a more descriptive term we prefer, non-coevolved organisms (NCOs).

As part of the pilot project, the IRRI Conference participants initially selected the particular crops to be evaluated, or stratified, and then enumerated the risk-related characteristics, or traits, to be considered in order to estimate overall risk.

³⁴⁵ Barton, John, John Crandon, Donald Kennedy, and Henry I. Miller, “A Model Protocol to Assess the Risks of Agricultural Introductions,” *Nature Biotechnology*, Vol. 15, No. 9, September 1997, pp. 845-848.

Organisms to be included in the stratification were selected to ensure that the final list would be diverse as to the type of crop, economic significance, and complexity of risk analysis. The stratification process required the group to reach consensus about the weighting of various factors that determine risk. Consensus was reached without serious difficulty on the most important factors. The participants agreed upon the following list of risk-based factors that would be integral to a model algorithm for field-testing and commercial approval of all introductions:

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

Each organism was assessed for all five factors, which enabled the group to come to a global judgment about the organism's risk category. Most of the common crop plants addressed were found to belong in negligible-risk Category 1, while some organisms were ranked in low but non-negligible-risk Category 2. One plant (cotton) was judged to be in Category 1 if it were field tested outside its center of origin, and Category 2 if tested within its center of origin.

It cannot be over emphasized that, in the evolution of this "Stanford Model," the factors taken into account in the analysis were indifferent to either the genetic modification techniques employed, if any (e.g., conventional breeding techniques vs. molecular methods of manipulation); or to the source(s) of the cultivar's genetic material (e.g., combining DNAs from phylogenetically distant organisms).

In other words, the group's analysis supported the position that the risks associated with field testing a genetically altered organism are independent of the process by which it was modified and of the movement of genetic material between "unrelated" organisms. The Stanford Model suggests the utility and practicality of an approach in which the degree of regulatory scrutiny over field trials is commensurate with

the risks – independent of whether the organisms introduced are "natural," exotics, or have been genetically improved by conventional methods or modified by gene-splicing techniques.

Regulators' treatment of field trials within the various categories could range from complete exemption or a simple "postcard notification" to a regulatory authority, to case-by-case review, or even prohibition (such as experiments currently with foot and mouth disease virus in the United States). Different national regulatory authorities might choose different regulatory requirements for the various risk categories; as discussed in the original paper,³⁴⁶ the model is sufficiently flexible that the stringency of regulation may vary widely, according to the preferences and needs of particular regulatory authorities – but always within a scientific framework. Under such a system, some currently unregulated introductions of traditionally bred cultivars and exotics considered to be of moderate or greater risk would likely become subject to review, whereas many currently reviewed gene-spliced organisms would likely become exempt. The introduction of such a risk-based system would rationalize significantly the regulation of field trials, and would reduce the regulatory disincentives that currently impede the use of in vitro genetic manipulation technologies for the benefit of agricultural development.

PLANTS IN THE FOOD SUPPLY

In 1992, the Food and Drug Administration published a notice in the Federal Register describing its official policy regarding foods derived from new plant varieties.³⁴⁷ This document, intended to clarify the FDA's position on the regulation of recombinant DNA technology and gene-spliced plants, explained that the "regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective characteristics of the food and the intended use." The policy reminded plant breeders and food producers that they had "an obligation under

³⁴⁶ Barton, Crandon, Kennedy, and Miller, 1997.

³⁴⁷ FDA, "Statement of Policy: Foods Derived From New Plant Varieties," *Federal Register*, Vol. 57, May 29, 1992, pp. 22,984-23,005.

the [Federal Food, Drug and Cosmetics Act] to ensure that the foods they offer to consumers are safe and in compliance with applicable legal requirements.” However, it treated gene-spliced and other foods no differently, and required scrutiny by regulators only when the products raised specific safety concerns. Thus, the agency’s approach was consistent with the consensus of the scientific community regarding the regulation of gene-spliced products. This approach was widely applauded as regulation that made sense, relied on scientific principles, protected consumers, and permitted innovation.

To guide developers of new plants on how to satisfy regulatory requirements, the FDA policy defined certain potentially hazardous characteristics of new foods that, if present, required greater scrutiny by the agency, and which could result in additional testing and labeling, or exclusion from commerce. In other words, characteristics related to risk – not simply to the use of one technique or another – would trigger heightened regulatory scrutiny. According to the FDA’s 1992 announcement, such characteristics include the introduction of genes that code for proteins (or mediate the synthesis of other added substances, such as fatty acids and carbohydrates) that differ substantially in structure or function from other substances typically found in the food supply. Heightened scrutiny by regulators would also be required if the genetic change altered a macronutrient (such as a new variety of citrus lacking vitamin C), caused a potent allergen to be presented in a milieu in which a consumer would not expect it (a peanut allergen in a potato, for example), or enhanced levels of a natural toxicant.

Thus, the FDA’s 1992 policy appeared to codify a risk-based approach to the oversight of new plant varieties. However, at the same time, and without the benefit of rulemaking or formal notification to industry, the agency created a “voluntary consultation procedure,” in which producers of gene-spliced plants were expected to consult with the agency before marketing their products. Without exception, they did so. Currently, thousands of food products in U.S. supermarkets contain gene-spliced whole foods or ingredients that have been regulated under the FDA’s formal 1992 policy and informal

consultation procedure. None has ever been shown to cause harm to human health.

In January 2001, the agency proposed to make mandatory the voluntary consultation procedure. If issued as a final rule, this would require developers of new plant varieties prepared with gene-splicing techniques – but virtually no others – to notify the FDA and supply large amounts of information before the plants could be marketed.³⁴⁸ The data requirements of the new policy are excessive, and the review process subjects food producers to the political and bureaucratic vagaries of the federal review process.³⁴⁹ The FDA lists nine categories of obligatory information whose level of detail is far greater than would be required (or could possibly be met) for food products made with less precise, less sophisticated techniques. Consider the example of *Triticum agropyrotriticum* described above, a non-gene-spliced “species” created by combining all the genes from bread wheat and a wild grass called quackgrass. New genetic constructions such as this are, as a class, exempt from all premarket regulations, while new gene-spliced varieties are, as a class, subjected to a de facto premarket approval requirement.

The reversal of the FDA’s scientific and risk-based approach to food regulation and the abandonment of a 20-year old commitment not to discriminate against gene-spliced products are unfortunate. The long-term result will be reduced use of a promising technology, diminished choices for farmers and consumers, higher food prices, and lower overall food safety. California, an important agricultural state, but one that does not grow significant amounts of commodity grain crops – which have been the primary focus for gene-splicing improvements by big agribusiness companies – will disproportionately bear the burden of these limitations; in other words, regulation makes the application of gene-splicing techniques too expensive to be used widely on the fruits, nuts, and vegetables widely grown in California.

³⁴⁸ FDA, “Premarket Notice Concerning Bioengineered Foods,” *Federal Register*, Vol. 66, January 18, 2001, pp. 4,706-4,738.

³⁴⁹ Miller, Henry I., *Political Angles at the FDA*, Washington Times, December 7, 1998, A19.

The FDA explained its 2001 decision to change policy in part by the expectation that many future gene-spliced plant varieties could contain substances that are not known to have been previously present in the food supply. Even if this were the case, however, such eventualities were foreseen under the official 1992 policy, and they would elicit agency review. It is the consensus of the scientific and professional communities that the FDA could address recombinant DNA-modified plants generally within its existing rules and require premarket notice, consultation or review only for those specific new plant varieties that raise risk-related concerns. This would represent a more constructive approach to the regulation of new plant varieties, one that would not punish or discourage innovation.

In summary, regulation should focus on real risks and should not be triggered by the use of one technique or another. This approach has provided effective oversight for thousands of new biotechnology products, including foods, drugs, vaccines, and diagnostic tests. There was no reason – except politics – to make, or even to consider, such a change. The erstwhile, risk-based FDA policy toward gene-spliced and other novel foods had worked admirably. It involved the government only in those extraordinarily rare instances when products raised safety issues. The result was eight years of unprecedented opportunity for farmers, food producers, and consumers.

Public Attitudes Regarding Regulation

Representatives of the biotechnology industry have played an important role in the development of this excessively precautionary regulatory system – but it has not been a positive one. In the late 1980s and early 1990s, when the U.S. Department of Agriculture, Environmental Protection Agency, and Food and Drug Administration were considering their options for the oversight of the products of recombinant DNA technology, industry representatives actually requested heightened regulatory scrutiny for gene-spliced agricultural and food products, ostensibly in order to bolster public confidence in gene-spliced foods. (However, there was virtually no public resistance at that time, and industry leaders admitted privately that excessive regulatory requirements were a strategy to create market-entry barriers to competitors' performing research and development.)

In spite of two decades of excessive, precautionary regulation by federal agencies having been accompanied by ever-increasing public concerns and resistance about gene-spliced food, the industry lobbied in favor of the most recent change in FDA policy.

Although efforts should be made to reassure the public that gene-splicing techniques are in fact safer than more “traditional” methods of genetic modification, excessive regulation is not an appropriate way to do so. The application of an intentionally excessive degree of government regulation to quell public apprehension – a rationale invoked by FDA for its new policy – is neither a legitimate use of government power, nor likely, ultimately, to reassure consumers. As the president of a national consumer organization testified to a panel convened by the National Institutes of Health (NIH):

“For obvious reasons, the consumer views the technologies that are most regulated to be the least safe ones. Heavy involvement by government, no matter how well intended, inevitably sends the wrong signals. Rather than ensuring confidence, it raises suspicion and doubt.”³⁵⁰

The NIH panel agreed, concluding, “Intense government oversight tends to confirm public perceptions that biotechnology processes pose significant and unique dangers that should be feared.”³⁵¹

Societal oversight of risks is complex, to be sure, but when crafting regulatory approaches to mitigate them, regulators and legislators should be guided primarily by science, economics, law, and a respect for Constitutional rights, not by government's perceptions of public perceptions, which are mercurial and doubly subject to error and misinterpretation.

Several subjective factors can cloud thinking about risks and influence how non-experts view

³⁵⁰ Keating-Edh, Barbara, Testimony before the National Biotechnology Policy Board, *1992 National Biotechnology Policy Board Report*, National Institutes of Health, Bethesda, MD, 1992.

³⁵¹ *National Biotechnology Policy Board Report*, National Institutes of Health, Office of the Director, Bethesda, MD, 1992.

them. Studies of risk perception have shown that people tend to overestimate risks that are unfamiliar, hard to understand, invisible, involuntary, and/or potentially catastrophic – and vice versa. Thus, they overestimate “threats” they cannot readily see, such as electromagnetic radiation and trace amounts of pesticides in foods, with a degree of uncertainty and fear sometimes verging on superstition. Conversely, they tend to underestimate risks whose nature they consider to be clear and comprehensible, such as using a chain saw or riding a motorcycle.

These distorted perceptions complicate the regulation of risk, for if democracy must eventually take public opinion into account, good government must also discount heuristic errors or prejudices. Edmund Burke emphasized government’s pivotal role in making such judgments: “Your Representative owes you, not only his industry, but his judgment; and he betrays, instead of serving you, if he sacrifices it to your opinion.” Government leaders should lead, by making decisions that are rational and in the public interest even if they are unpopular at the time. This is especially true if, as is the case for most federal and state regulators, they are granted what amounts to lifetime job tenure in order to shield them from political manipulation or retaliation. In the area of biotechnology regulation, as discussed above, regulators have failed Burke’s test of earning the public trust.

CONCLUSIONS

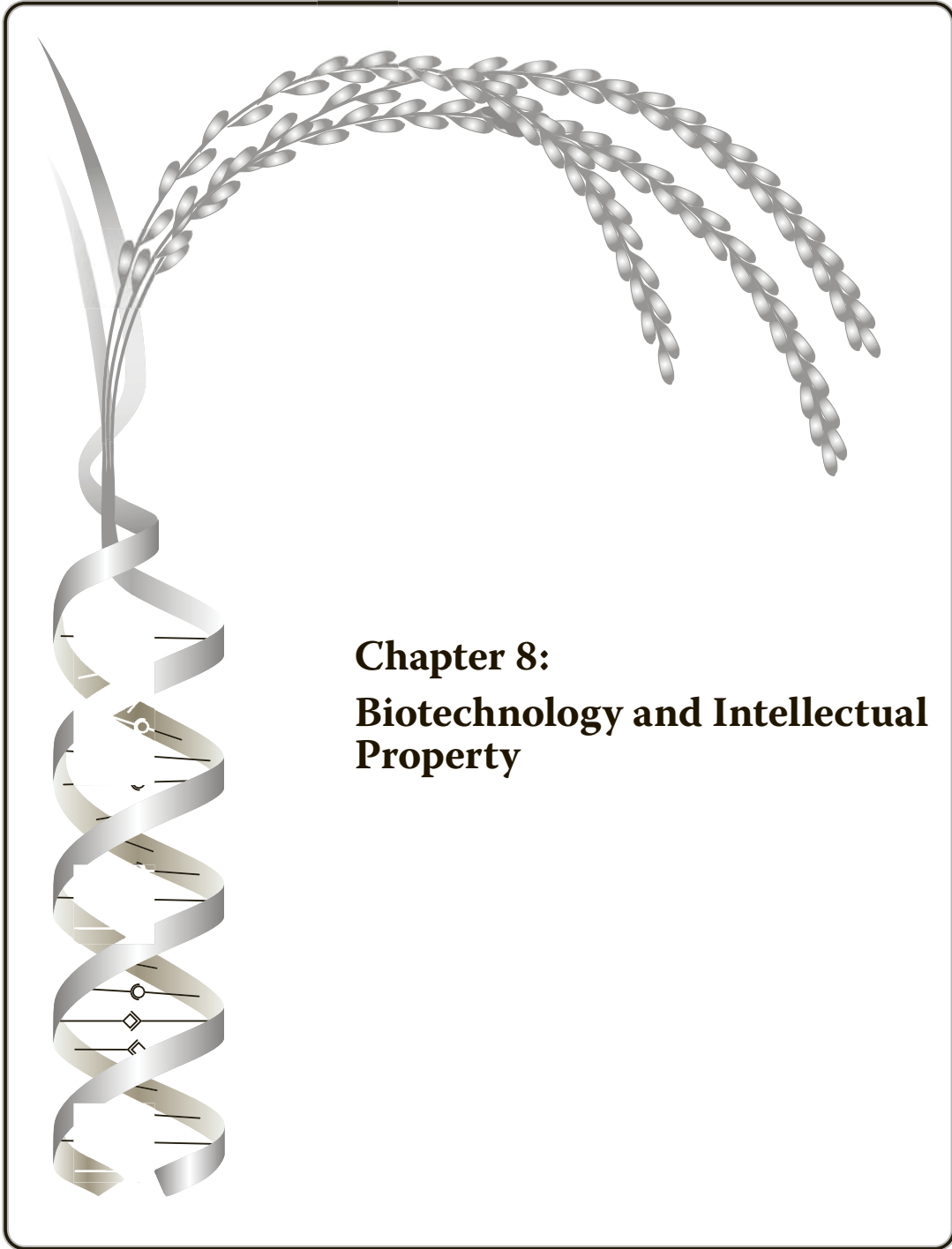
History offers compelling reasons to be cautious about societal risks, to be sure. These include the risk of incorrectly assuming the absence of danger (false negatives), overlooking low probability but high impact events in risk assessments, the danger of long latency periods before problems become apparent, and the lack of useful remediation opportunities in the event of an adverse event. Conversely, there are compelling reasons to be wary of excessive precaution, including the risk of too readily detecting a non-existent danger (false positives), the financial cost of testing for or remediating low-risk problems, the opportunity costs of forgoing net-beneficial activities, and the availability of a contingency regime in the event

of adverse events. The challenge for regulators is to balance these competing factors in a way that reduces overall harm to public health. This kind of risk balancing is often conspicuously absent from precautionary regulation, of which there are few more conspicuous examples than oversight of recombinant DNA technology.

It is also important that regulators take into consideration the ambient level of restraint generally imposed by society on individuals’ and companies’ freedom to perform legitimate activities such as scientific research. In the Western democratic societies, we enjoy long traditions of relatively unfettered scientific research and development, except in the very few cases where bona fide safety issues are raised. Traditionally, we shrink from permitting small, authoritarian minorities to dictate our social agenda, including what kinds of research are permissible, and which technologies and products should be available in the marketplace.

Application of the precautionary principle in a number of areas has resulted in unscientific, discriminatory policies that inflate the costs of research, inhibit the development of new products, divert and waste public- and private-sector resources, and restrict consumer choice. The excessive, discriminatory and poorly conceived regulation of recombinant DNA technology applied to agriculture and food production is a prominent example. Further encroachment of the precautionary principle into this and other areas of domestic and international health and safety standards will create a kind of “open sesame” that government officials could invoke fearlessly whenever they wished arbitrarily to introduce new barriers to trade, or simply to yield to the vocal demands of a radical, anti-technology constituency.

The controversies over gene-splicing applied to agriculture and food production are, for the most part, pseudo-controversies. The science is clear. The public policy implications of continuing to apply flawed regulatory paradigms are clear. The appropriate approaches to regulatory oversight are clear: risk-based approaches to oversight are available. All that is uncertain is whether we will find the political will to go where science, common sense and the public interest dictate.



**Chapter 8:
Biotechnology and Intellectual
Property**

Chapter 8: Biotechnology and Intellectual Property

Brian D. Wright, University of California, Berkeley

In general, the changes in biotechnology and intellectual property protection are mutually reinforcing. Biotech research gives value to intellectual property rights (IPRs) in agriculture by enabling the enforcement of those rights, and by making those rights valuable enough to be worth enforcing in major crop lines. The intellectual property rights, in turn, make it possible for research organizations to capture more of the value generated by biotech research. Thus, they make private enterprise possible for the first time in many broad research areas in agriculture and the health sciences, and they present universities, cooperatives, and other public and non-profit institutions with the option of licensing or selling research outputs in this area, rather than giving their results away for free.

As the scope and power of IPRs in biotechnology has grown, its international reach has expanded. The innovation response has been impressive. The events of the past two decades have also affected the kinds of research that are done, and who does the research.

The facilitation of private research makes possible a better alignment of research responsibilities and beneficiaries. Since a large share of the output of many major California crops is exported from the state, much of the in-state benefits from research go to landowners and other input suppliers. Commodity groups are very well informed about their research needs, and well motivated to support their provision. Thus, partnerships between commodity groups and public researchers make sense if the burden is shared equitably and roles are allocated wisely.

One key challenge is to ensure that such collaborators can continue in a world in which many of the key enabling technologies have been privatized, and access to these technologies is risky, expensive, or even blockaded. Another challenge is to ensure that the creative role of public researchers and private agricultural

biotechnology startups is not suppressed by anti-competitive use of patent rights by larger, well-established corporations with substantial market power. Furthermore, policymakers should try to ensure that the value of public research output, such as new conventionally bred or genetically transformed cultivars, is not hijacked by private oligopolists who insert key complementary inputs, such as pesticidal or herbicide-tolerance genes, that are protected by patent portfolios. Thus, IPR poses challenges as well as opportunities for agricultural researchers. Some initiatives of interest to California policymakers are referenced in the conclusion.

THE REVOLUTION IN INTELLECTUAL PROPERTY PROTECTION

Historically, intellectual property rights had little relevance for agricultural research. In the 19th and early 20th centuries, machine-related inventions, produced mainly by farmers and mechanics, were often protected by utility patents, which usually at best reap modest financial rewards. Inventions were in general easily copied, and licensing difficult to enforce.³⁵² Biological innovations had no legal protection. The germplasm (seeds and other breeding materials) of major agricultural crops was available at low or zero cost. In the 20th century, the first major innovation in intellectual property rights for agriculture was the Plant Patent Act.

Plant Patents

The United States Plant Patent Act of 1930 gave protection from unauthorized cloning to many clonally propagated plants for the life of the patent. The protection applied only to clonally propagated varieties such as fruit trees or tubers. This protection was useful principally in horticulture,

³⁵² Eli Whitney's famous cotton gin was patented, but so widely copied that Congress felt obliged to reward him with a prize to compensate him for his invention.

and has been important for strawberry breeding in California, for example.

Plant Breeders' Rights (PBR)/Plant Variety Protection Certificate (PVPC)

Some restrictions were placed on the use of sexually propagated seed for replanting via the introduction of the Plant Variety Protection Certificate (PVPC) in the Plant Variety Protection Act of 1970. PVPCs are administered by the United States Department of Agriculture. They protect a new, uniform, and distinct variety against unauthorized sale for replanting, and restrictions on replanting saved seed by producers have been strengthened over time in the United States, but are still difficult to enforce. However, use for breeding new varieties is not protected. An exception is the breeding of a variety "essentially derived" from a protected parent. This exception might cover a cultivar differing by a small amount of transgenic DNA, but its scope has yet to be established. In a notorious case, a soybean cultivar was approved as distinct based only on its blue flower color, a trait not generally considered meaningful in commercial soybeans.

Even if stronger protection had been given to seed producers against unauthorized use for new varieties, enforcement would have been hampered by the difficulty of identifying proprietary germplasm as the parent of a new commercial variety. Until the advent of biotechnology, only hybrid seeds that did not breed true were protected against this type of misappropriation. In the case of United States corn, as the most prominent example, protection via hybridization was strong enough to foster the growth of a profitable private seed industry in the 1930s, well before the strengthening of effective legal intellectual property protection of plants.

In the pre-1980 scientific environment, the post-1980 IPR revolution would have been almost irrelevant for much of agricultural research. For example, defense of patents owned by breeders or seed sellers requires proof of infringement. By serendipity, the revolution in analysis of genetic material ushered in by the Cohen-Boyer patent of 1980 produced a set of technologies well suited to detection of unauthorized reproduction or breeding via analysis of seeds, leaves, or other

genetic evidence. These methods also have been effective in enforcing state trade secret law as a protection of inbred parent lines used in hybrid corn breeding.

Trade Secret

Advances in biotechnology have added strength to this traditional means of protection available under state law in the United States. Using the "genetic fingerprinting" made possible by the early advances in biotechnology, Pioneer Hi-Bred International was able to win a lawsuit against Holden's Foundation Seeds under Iowa's trade secret law, and received \$47 million in damages (*Pioneer Hi-Bred v. Holden Foundation Seeds*, 35F3d1226, 1994). If a seed is to qualify for trade secrecy protection, it must be protected from acquisition by others. This may be feasible with "in-house" parent lines of commercial hybrids. But it is impossible to protect as a trade secret the information in the commercial seeds sold to farmers.

(Utility) Patents

Patents protect inventions and confer a legally enforceable right allowing their owners to exclude others from practicing the invention described and claimed in the document. However, these rights apply only for a limited period of time, generally 20 years from the date of filing, and only in a specific legal jurisdiction, and the scope of the property protection is circumscribed by the claims made in the patent. To be patentable, an innovation should be novel, non-obvious, embodied in a physical form (not just an idea), and described in a way that can be implemented in practice by a person ordinarily skilled in the relevant arts. Patents cover both processes and products ("compositions of matter"). In 1980, the Supreme Court ruled that patents could apply to life forms, and subsequent rulings established that plants, animals, and DNA sequences were patentable.

In agricultural biotechnology, patents now cover innovations in many technologies, such as:

- *Germplasm*, including plant seeds, cuttings, and tubers, and also bacteria and fungi, and animals such as transgenic mice;
- *Trait specific genes*. These include input traits such as the well-known "Roundup Ready"

and “Liberty Link” herbicide tolerance traits, and genes from *Bacillus thuringiensis* (*Bt*) for insect resistance. Other genes confer agronomic traits such as tolerance of abiotic stress, fungal or viral resistance, and cold tolerance. Other genes confer output traits such as delayed ripening, increased content of starch, oil, amino acids, proteins, vitamins, and minerals, or decreased content of traits that are harmful (for example, allergens) or contribute to environmental pollution (such as phytates that increase the environmental damage from manure);

- *Transformation technologies* by which a gene, which codes for a specific characteristic, is inserted into plant cells;
- *Promoters* which are used to control expression of the gene in plants;
- *Genetic markers* which are genes used in conventional breeding or in production of transgenics to identify the presence of a desired trait; and
- *Gene silencing or regulating technologies* that can be used to suppress or modify gene expression in plants.

Patents are awarded by national governments and the intellectual protection conferred by a patent extends only to the national jurisdiction in which the patent is awarded. To protect an innovation in more than one country, a patent must be awarded in each. The cost of obtaining a patent varies from country to country; the cost of obtaining protection in all important markets can be very substantial, as much as hundreds of thousands of dollars. Patent values are highly skewed, for example, the Cohen-Boyer innovation has earned more than \$100 million in license revenues, while most other patents generate income from zero to tens of thousands dollars. Most inventions that are patented have protection in just one or a few developed countries with large markets; the chance that many of the relevant biotech patents have been awarded in developing countries is currently small, even where patenting is available. But the availability of patenting is proliferating, as discussed further below.

Other Forms of IPR

Other traditional forms of protection that can be important for private firms include trademarks and copyrights. For researchers, the extent of protection provided by copyrights to owners of databases is a crucial issue and a bone of contention between the European Union (which offers stronger protection) and the United States.³⁵³

MEANS OF TRANSACTIONS IN IPRs

An IPR has value only if it permits profitable commercialization of the relevant technology. In general, enforcement hinges on the strength of the legal system and the cost of establishing and evaluating a claim that an IPR has been violated. We have seen that biotechnology can help prove violation, and can also combat it directly, as in the case of hybrid corn. Legal agreements are structured to reduce the transaction costs in transfers of IPR. They include:

Patent License

Patent licenses may be obtained on an exclusive or nonexclusive basis, and they may restrict the use of the technology. Research licenses are often cheaper and easier to get than commercial licenses, but they allow use only in research. Innovations achieved under a research license may be blocked for subsequent commercialization by the license holder, leaving the innovator in a weak bargaining position. Royalty payments can be in many forms, from an up-front lump sum to a running royalty depending on value or volume of production. A running royalty cannot be used to extend patent life. An owner of a patent on an enabling technology might ask for a license giving royalties for products generated from innovations achieved using the technology. Such “reach through” licenses are controversial, but might be a reasonable means of sharing risk and reward from an uncertain research path.

³⁵³ S. Maurer, P.B. Hugenhotlz & H. Onsrud, “Europe’s Database Experiment,” 294 *Science*, 2001.

Material Transfer Agreement (MTA)

An MTA is a contract for transfer and use of breeding inputs for deposit in a genebank, for research, or for commercial use. The transferred material must have some independent means of protection (e.g., patent or trade secrecy) to prevent its appropriation by third parties. In general, an MTA is a means of transferring material with “trade secret” protection, as embodied, for example, in various state laws in the United States. It may restrict the user’s rights to improvement, resale, or commercialization. MTAs are being used, for example, by the research centers of the Consultative Group on International Agricultural Research (CGIAR) to control the use of plant varieties held “in trust” on behalf of the countries of origin in their genebanks. If access to the materials is not otherwise available, this protection may be effective in preserving the provider’s rights to the germplasm.

Bag-label Contract

An implicit contract is described on a bag label. The buyers of the product agree to comply with the contract when they break the label to open the bag. Thus, a bag-label contract seems analogous to the “shrink-wrap” contract common in software transactions. If use of the seed for breeding is found to violate such an implicit contract, then bag-label contracts are an additional means of protection of intellectual property. The strength of such contracts is not yet firmly established.

Technology Use Agreement

Technology use agreements are an innovation in property rights enforcement. They control the right to plant a given seed type on a specific area of land and have been implemented and enforced by producers of agronomic traits in the United States over the past few years. Their provisions can also include restrictions on the use of proprietary traits in the creation of new varieties, as well as permission for access to the relevant property to check for violations. The latter is not popular with farmers.

Genetic Use Restriction Technology (GURT)

Despite the expanding scope of legal protection, legal enforceability and its cost are still major issues. This is especially true at the farm level. Even in the developed institutional environment

of the United States, it is not cost-effective to sue farmers in court for IPR infringement, because the sums at stake and the limits on farmers’ assets are usually less than the cost of the suit. Such actions can be justified only by their deterrent effects on others.

As an alternative to legal means, the biotechnology sector is currently developing technological means of appropriating the returns to innovation. These technologies are collectively dubbed Genetic Use Restriction Technologies (GURTs), but the earliest form is more widely recognized by the nickname “Terminator Genes,” which enable the control of plant reproduction and inducible traits. That is, they allow seed producers to turn “on” and “off” the traits of a plant, including its reproductive functions. Commercial deployment of these technologies may happen as early as 2006 (U.S. Department of Agriculture (USDA) 2001). These methods render the seed unsuitable for replanting or suppress the expression of certain introduced traits in saved seed.

There are two lines of GURTs under development, variety-level GURTs (V-GURT) and trait specific GURTs (T-GURT). In 1998, the first V-GURT patent was awarded jointly to the USDA and Delta & Pineland (D&PL), the largest U.S. supplier of cottonseed. In brief, the USDA/D&PL technology involves inserting three transgenes (toxin gene, site-specific recombinase gene, and recombinase repressor gene) into the plant DNA. The genes are connected so that (a) the repressor gene prevents the recombinase gene from functioning, (b) the recombinase gene, if it functions, allows the toxin gene to activate, and (c) the toxin gene produces a toxin that kills the embryo in the seed so the seed cannot germinate.

The seed producer can control the system by spraying the first generation seed with a regulator. The regulator then inactivates the repressor gene. Since the repressor gene doesn’t function, the recombinase gene is allowed to do its job, as in step (b) above. If the seed producer wishes to protect the intellectual property embedded in the seed, the seed is sprayed with the regulator before delivery to the farmer. This type of protection has generated substantial international opposition

on various grounds from farmers and non-governmental organizations. One major concern is the possibility that a neighbor might have his crop sterilized by drifting pollen, so that if the seed is saved and replanted the next crop is ruined.

T-GURTs do not present this problem. There are two possible ways in which they can be designed. In the first instance, a chain of genes similar to the one described above is constructed. The system can be programmed so that the toxin gene deletes a "trait" gene instead of killing the embryo. Thus, if the seed is sprayed with regulator before delivery to the farmer, the first generation seed will produce the trait embodied in the trait gene, but the second generation will not.

In the second case the farmer, who applies an "activator" compound to the plant or seed, activates the T-GURT. The system can be designed so that subsequent generations of the seed will contain the trait gene, but in an inactive state. Thus, use of the trait in a given year requires the farmer to purchase and apply the activator in that year. In addition, USDA (2001) suggests a T-GURT that can be activated by the farmer's spraying of the "standing crop" with the activator. It is not clear if such a technology is feasible, or even if it were feasible, whether the timing of application of the activator would be flexible. If the timing of application were flexible, this would confer option value upon the T-GURT-protected trait. That is, the farmer could wait until he knows the trait, such as disease resistance, is needed before purchasing the activator. This could possibly help prevent resistance buildup.^{354, 355}

³⁵⁴ Srinivasan, C.S. and C. Thirtle, "Impact of Terminator Technologies in Developing Countries: A Framework for Economic Analysis," Presented at the International Consortium on Agricultural Biotechnology Research's (ICABR) 4th International Conference, Economics of Agricultural Biotechnology, Ravello, Italy, August 24-28, 2000.

³⁵⁵ Commission on Genetic Resources for Food and Agriculture, "Potential Impacts of Genetic Use Restriction Technologies (GURTs) on Agricultural Biodiversity and Agricultural Production Systems," First Session of Working Group on Plant Genetic Resources for Food and Agriculture, Rome, July 2-4, 2001.

INTERNATIONAL PROLIFERATION OF PROPERTY RIGHTS PROTECTION FOR AGRICULTURAL BIOTECHNOLOGY

As the leader in world innovation and in international rulemaking for trade and intellectual property, the United States laid the legal and scientific foundations for the biotech revolution in the 1980s. In the early 1990s, IPR took center stage at the international level when United States negotiators insisted, in the Uruguay Round of the GATT negotiation (which gave rise to the establishment of WTO), on expansion and strengthening of intellectual property protection internationally. The result was the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) (1994). TRIPS was expressly designed to ensure that intellectual property rights could be applied to virtually all technologies, especially those which had previously been declared unsuitable for monopoly rights at the national level, including pharmaceutical products, biological materials, and other life forms including plants and micro-organisms.

Article 27.3(b) of TRIPS mandates that all members of the WTO adopt a patent system or other "*sui generis*" system of intellectual property protection to protect plants and other life forms. Developed countries have, in most cases, opted for patent protection. In 1998, the European Parliament approved a proposal for a European Directive on the Legal Protection of Biotechnological Inventions to be implemented by member countries within two years. This directive, which was the subject of ongoing controversy, allowed patenting of genetic material including groups of plant or animal varieties for which application of an invention is feasible.

In many countries, protection includes a system of plant variety protection similar to the 1994 revision of the United States PVPC, in line with the 1991 Convention of the International Union for the Protection of New Varieties of Plants (UPOV), which came into force in 1998. It is commonly understood that *sui generis* systems of plant variety protection similar to that provided under UPOV will be acceptable under TRIPS, and many developing countries are adopting such systems.

The Rise of Farmers' Rights

As IPR over plants has been extended in developed countries, nations that provided the domestic seed varieties ("land races") used in breeding have responded by attempting to assert their claims to the basic genetic material derived from their traditional varieties under the name "Farmers' Rights." Farmers are not surprisingly unhappy about a system that gives the private sector free access to their landraces for breeding, but demands payment for the genetic modifications they add. Exactly how such rights should be recognized is left unclear. They do not seem to be amenable to protection by the usual IPRs that confer rights to individual inventors or institutions such as utility patents, PVPC's, or trade secrecy. Some form of collective rights seems more appropriate, but is proving difficult to put into practice.

The concept of Farmers' Rights resulted from debates that started in 1979 in FAO, concerning the asymmetric benefits derived by the farmers and communities who fostered the development and conservation of landraces and indigenous varieties, and the holders of IPRs over modern biotechnology. The International Undertaking on Plant Genetic Resources, the first comprehensive international agreement dealing with plant genetic resources for food and agriculture, was adopted by the FAO Conference in 1983, as an instrument to promote international harmony in matters regarding access to plant genetic resources for food and agriculture. One hundred thirteen nations have adhered to the Undertaking, which seeks to "ensure that plant genetic resources of economic and/or social interest, particularly for agriculture, will be explored, preserved, evaluated, and made available for plant breeding and scientific purposes". It is monitored by the Commission on Genetic Resources for Food and Agriculture (CGRFA).

The implications of the Undertaking have evolved via a series of agreed interpretations, in the form of three FAO Conference resolutions, which are now annexed to it. They were intended to achieve a balance between the products of biotechnology (commercial varieties and breeders' lines) on the one hand, and farmers' varieties

and wild material on the other, and between the interests of developed and developing countries, by balancing the rights of breeders (formal innovators) and farmers (informal innovators). Resolution 5/89 recognized that Plant Breeder's Rights, as provided for by the International Union for the Protection of New Varieties of Plants, were not inconsistent with the Undertaking, and simultaneously recognized farmer's rights defined in Resolution 5/89 as "rights arising from the past, present and future contributions of farmers in conserving, improving, and making available plant genetic resources, particularly those in the centers of origin/diversity." Resolution 3/91 states, "Farmers' Rights will be implemented through international funding on plant genetic resources, which will support plant genetic conservation and utilization programs, particularly, but not exclusively, in the developing countries". The sovereign rights of nations over their genetic resources were recognized in Resolution 3/19, and it was agreed that Farmers' Rights would be implemented through an international fund for plant genetic resources.

The Commission had requested the preparation of a rolling Global Plan of Action (GPA) on Plant Genetic Resources for Food and Agriculture in 1993, in order to identify the technical and financial needs for ensuring conservation and promoting sustainable use of plant genetic resources. In 1996, 150 countries formally adopted the GPA. They also declared that it was important to complete the revision of the Undertaking. The GPA and its implementation is a subject of discussion in the Undertaking. The other key elements currently under discussion in the negotiations include the scope and access to plant genetic resources; the fair and equitable sharing of benefits arising from the use of plant genetic resources for food and agriculture; and the realization of Farmers' Rights. Countries have agreed that the Undertaking should maintain a multilateral system of access and benefit sharing that meets the specific needs of agriculture. The Undertaking is at the crossroads where agriculture, environment, and trade meet. The revised Undertaking, to be approved in November 2001, is a major international instrument reflecting the significance of access and benefit

sharing as the basis for continued and sustainable utilization of plant genetic resources for food and agriculture.

About a year before the TRIPS first came into force in underdeveloped countries, the 1993 Convention on Biological Diversity (CBD) issued a call for the conservation and sustainable use of biological diversity. Signatories of the CBD can make an international commitment, as legally binding as TRIPS, but most of the commitments are more weakly phrased. Though the implications of the CBD are still being worked out, some researchers argued that the rights and objectives established by the agreement conflict with TRIPS. Yet both treaties provide legally binding obligations for governments. One hundred sixty-eight nations have signed the CBD, but the United States has not. Well over 130 are committed to both treaties.

The Cartagena Protocol on Biosafety is another international agreement, negotiated under the auspices of the CBD, which, if ratified by 50 parties, will affect trade in genetically modified products. At present, only 13 countries are parties to the Protocol. Should the United States become a party, it would be responsible for policing illegal or accidental release of modified organisms in California, presumably by withholding funds to the State or by other measures. Since the Protocol clearly conflicts with the goals of the WTO, further evolution of international coordination in this area is likely, and should be followed closely by the California Legislature.

THE INNOVATION RESPONSE TO STRONGER INTELLECTUAL PROPERTY RIGHTS

In the early 1990s, the environment was uniquely favorable for innovations in agricultural biotechnology. Funding for the basic science on which it relies was greatly increased by huge increases in federal budgetary allocations to the National Institutes of Health. Opportunities for innovation abounded. Most of them were freely available for exploitation, and commercialization of further innovations encountered few obstacles. Pharmaceutical firms, domestic and European, transformed themselves into "life science" conglomerates, divested of commodity chemical

divisions and anticipating synergies between newly integrated agricultural biotechnology activities and their pharmaceutical divisions. Agricultural biotechnology startups proliferated in the United States, and nonprofit institutions, and their researchers, looked upon their agricultural biotech research in a new light.

Breakthroughs in recombinant DNA technology, including the Nobel Prize-winning work of UCSF's Herb Boyer and Stanford University's Stanley Cohen, started the revolution in biotechnology. Their key innovation was patented, but licensed widely at low cost. Basic research in the United States, funded largely by the National Institutes of Health, established the fundamental techniques and processes that led to the commercial use of biotechnology. Many corporations applied for broad patents on genes, for medical and other purposes as well as agricultural uses. The U.S. Patent and Trademark Office received 4,000 patent requests for nucleic acid sequences in 1991, mushrooming to over 500,000 in 1996.

Passage of the Bayh-Dole Act in 1980 gave researchers the right to retain title to the material and products they invented under federal funding in non-defense areas. This allowed the profitable privatization of biotechnology to begin in the academic world. Since then, the output of public researchers has been increasingly privatized, in the sense that others can use it, for at least some purposes, only with the consent of the relevant property rights owner.

The result of the new legal and scientific opportunities was a proliferation of new applications of biotechnology in agriculture and related industries, including prominently herbicide-tolerant soybeans, corn, cotton and canola, and insect-resistant corn and cotton. These and other innovations are covered elsewhere in this report.

THE DOWNSIDE OF IPR PROTECTION

Patents and other means of IPR protection create the strongest incentive to research when there are no prior IPR claims on the inputs or methods used, or on the results of their use. Such “freedom to operate” was broadly available in the 1980s. In effect, in this first round of expanded patentability, patentees capture value that previous research created. As patents on research tools and products proliferate, the restrictive force of the monopoly conferred by prior patents comes to bear on the next generation of research³⁵⁶ with implications that are currently the subject of theoretical research.³⁵⁷ This began to happen in the 1990s. The impacts have been dramatic in terms of transactions in IPR, the structure of the market for seeds and other related products, the contributions of biotech startups, and access to key technology by nonprofit research organizations.

Transactions Costs in IPR

Public researchers are realizing now that the availability of intellectual property protection for public research output is a mixed blessing when research has proceeded beyond the first round of privation technology. Patents and other means of IPR protection create the strongest incentive to research when there are no prior intellectual property claims on the research results. In effect, the patentee captures value that previous research created. But high transaction costs become evident in the second round of private research, which uses materials or processes with prior proprietary protection.

In addition to the cost of the rent transfer to prior patent holders, the costs of actually consummating licensing deals may be significant. These include the costs of discovering the existence, nature, and ownership of prior patent claims. (Indeed it might be impossible to ascertain the nature of patent applications at any

cost, until they are published, at least 18 months after application.) They also include the costs of negotiating rights to use or acquire the relevant intellectual property in a dynamic market, where the number of negotiating parties is small, and values are not clearly established and constantly changing.

The transaction costs involved in obtaining freedom to operate in the necessary inputs and processes (genes, promoters, markers, germplasm, transformation technology, etc.) could be very significant. For example, many millions of dollars and much managerial effort have been spent on legal disputes over proprietary technology related to control of insect pests using transgenic plants expressing *Bt* genes. It is no coincidence that many of the corporations involved in this technology chose attorneys, not plant breeders or biologists or marketers, as their CEOs.

The recent experience in biotech shows that IPRs give unambiguous, strong incentives for initial research. However, in their current forms they are not nearly as good at facilitating transactions in the second-round products of research. The transactions are not low-cost and they can be very unreliable, especially when overlapping patents or patent applications are involved. In fact, avoidance of transaction costs has been an important motivation for many mergers involving private firms in the agricultural biotechnology industry in recent years.

Transformation of the Market for Seeds and Related Products

Historically, the dominant player in producing new crop varieties has been the public sector, including in the past half-century international nonprofit organizations with substantial public sector support such as the research centers in the CGIAR. Starting in the 1980s, the biotech companies formulated a strategy of selling crop protection traits to seed producers via arms-length IPR transactions. Seed producers were to become retailers of crop protection beyond natural genetic resistance. A few large seed producers also began their own biotech initiatives. Thus, some seed producers were able to develop products that substituted for certain insecticides or favored one

³⁵⁶ Heller, M.A. and R.S. Eisenberg, “Can Patents Deter Innovation? The Anticommons in Biomedical Research,” *Science* 280, May 1, 1998, 698-701.

³⁵⁷ Koo, Bonwoo and Brian D. Wright, *Economics of Patenting a Research Tool*, International Food Policy Research Institute and University of California, Berkeley, December 2001.

herbicide at the expense of others, while others licensed these products from biotech companies.

The first wave of integration in the inputs market brought agricultural chemicals and biotech together. By the late 1980s, the most far-sighted pesticide and herbicide producers saw the logic of becoming “life science” corporations, conducting their own biotech research and buying up their biotech competitors, in the human health area and in agricultural biotech.

Agricultural biotech came increasingly under the control of a few major life science players. Monsanto, the leader in this trend, saw the opportunity to expand its increasingly profitable Roundup (glyphosate) herbicide market, and extend its profitability after its patent expired, by developing or acquiring rights to glyphosate-resistance genes. It also was a leader, with Mycogen and Ciba, in developing *Bt* pesticidal transgenic cultivars. Since Monsanto was weak in other herbicides and in pesticides, the markets Roundup stole would be those of its competitors.

Around late 1995, before seed producers had significant transgenic sales, the strategy of the most far-sighted producers of crop protection chemicals started to change. As the transaction costs associated with licensing became more apparent, the idea of profiting from licensing of traits protected by IPR began to be supplanted by the strategy of integrating forward into the retail seed market. A wave of high-priced acquisitions of independent seed producers began with initial minority equity investments.

In 1998, the supplier integration became more complete via more mergers and acquisitions. Biotech for herbicide tolerance, biotech for insect protection, and biotech for output traits were all being incorporated in the seed that was sold to the farmer. Crop protection chemicals, some complements and others substitutes for the transgenic traits were now produced by some of the same companies that sell the seed to the farmer. Since 1999, life science companies have become disenchanted with agriculture because of low commodity prices, lack of anticipated technical synergies with human health biotech, and adverse consumer reaction to transgenics in

major export markets. As part of a new wave of mergers, life science firms have announced plans to divest their ag biotech divisions and concentrate on pharmaceuticals. If these plans are successfully executed before another change in corporate becomes the fashion, the agricultural divisions are likely, when spun off, to increase in the size of their agricultural presence and the range of products in which they have market dominance.

Farmers had long become accustomed to dealing with seed oligopolies, crop consultants, crop herbicide and insecticide oligopolies, fertilizer oligopolies, and/or processing oligopolies. But the farmer was primarily responsible for coordinating his technological choices from a large number of alternative combinations of suppliers.

Now oligopolists are moving towards mergers that could integrate the whole gamut on the input and the output side of agriculture. It is not just that any one of the industries that farmers deal with is becoming more concentrated; it is that firms in different industries are now tending to merge into a single enterprise that could become an oligopolistic one-stop shop for farmers’ inputs and outputs. This phenomenon is largely being driven by attempts to get around contracting problems associated with IPR for new biotechnologies, to capture the maximum value inherent in novel output traits, to maintain the market price of crop protection formally offered in chemical form and now embodied in the DNA of the seed, and generally to protect and, if possible, increase the private returns to crop protection and other services in the face of rapid technological change.

Freedom to Operate: The Special Challenge for Nonprofit and Start-up Researchers

A serious impediment to public research on genetically engineered crops arises when the key technologies and/or materials including genes, markers, promoter, and means of transformation are not obtainable from patent holders on reasonable terms. Plant breeding is a cumulative science. As patents on research tools, processes, and products proliferate, the restrictive force of monopolies conferred by these patents comes to bear on the next generation of research. The diversity of innovations utilized in modern cultivar development can result in

a balkanization of competing claims that can seriously hinder subsequent innovation. For example, the transgenic vitamin A rice, currently under development as Golden Rice®, incorporates technology that is based on at least 70 patents with 32 owners.³⁵⁸ In such cases, where ownership of rights is diffuse and uncertain, the multilateral bargaining needed to access all of these rights can become difficult if not impossible. In the case of vitamin A rice, major intellectual property holders have made their technologies freely accessible for poor farmers in developing countries. This has been well publicized.³⁵⁹ It is less widely recognized that most of the patents are not valid in those countries anyway.³⁶⁰

In the United States and some other developed countries, some university research projects designed to produce new crops with modern biotechnology have been shut down because of refusal of IPR-holders to permit commercialization of varieties incorporating their intellectual property. In one example, UC researchers, with industry support, successfully created a tomato variety genetically engineered to express the university's endoglucanase gene to retard softening and improve shelf-life characteristics. However, the promoter they used was one for which a patent application surfaced during the development of the new cultivar. The patentee, a private corporation, refused to negotiate terms for the use of its embodied technology for commercialization of the cultivar. The research and development effort came to naught, shattering

the confidence of the commodity group in the capacity of the university to successfully breed and commercialize new transgenic cultivars.

More recently, a similar refusal to negotiate was encountered when a transgenic barley with good herbicide tolerance was developed during a research project. The owner of the relevant herbicide tolerance patent (a different company than in the previous example) refused to negotiate commercialization rights, and indeed refused to discuss developing the germplasm itself. A similar failure of commercialization due to refusal of freedom to operate has been encountered in development of herbicide-tolerant turfgrass and of an herbicide-tolerant lupin in Australia.

Economists tend to believe that when there are gains to be made from a trade, the trade will occur. Why then did the parties fail to find a mutually satisfactory solution in the above examples? In an economic tautology, the "transaction costs" must have been too high.³⁶¹ Perhaps the public sector negotiations had unrealistic expectations regarding private-sector largesse. Maybe the owner of the key technology saw no way to protect itself from liability or from damage to its reputation, in the event that the developed products were mismanaged or did not perform. Or it could be the expected financial gains, given the size of the market, were less than the cost in time and money to the corporation of making and enforcing an agreement. Or perhaps the patent holder saw no reason to help out a potential competitor in the tomato market, who might be willing to sell at a lower price.

IMPLICATIONS FOR CALIFORNIA PRODUCERS

As is well known, private-sector investment in agricultural research now matches public investment in major developed countries including the United States. But private investment has focused on a small number of high-value crops, mainly corn, soybeans, and cotton. In all three crops, transgenics incorporating herbicide

³⁵⁸ Kryder, R.D., S.P. Kowalski, and A.F. Krattinger, The Intellectual and Technical Property Components of Pro-vitamin a Rice (Golden Rice®): A Preliminary Freedom-to-operate Review, ISAA, Briefs No. 20, Ithaca, The International Service for the Acquisition of Agri-biotech Applications, 2000.

³⁵⁹ Tait, N. and M. Wrong, "Deal Offers Free GM Rice to Poor Farmers while Rich have to Pay," *Financial Times* (London, May 16), 2000, as reproduced by Ag Biotech Infonet, http://www.biotech-info.net/deal_offers_free_rice.html.

³⁶⁰ Binenbaum, E., C. Nottenburg, P.G. Pardey, B.D. Wright, and P. Zambrano, "South-North Trade, Intellectual Property Jurisdictions, and Freedom to Operate in Agricultural Research on Staple Crops," EPTD Discussion Paper No. 70, International Food Policy Research Institute, Washington, D.C., December 2000.

³⁶¹ Wright, B.D., "Public Germplasm Development at a Crossroads: Biotechnology and Intellectual Property," *California Agriculture*, 52(6), November/December 1988, 8-13.

tolerance or *Bt* pest-resistance genes have been huge market successes for some firms, and widely adopted by growers.

California's agriculture, though the highest in value of any state, is diversified among many crops. Though these tend to be of high value per acre, the total value of each pales in comparison to the national corn or soy market. California's main crops have not been the prime targets of genetic engineering efforts by large agricultural biotechnology companies. Although recent adverse publicity, especially in export markets, has discouraged new applications of biotechnology and in particular transgenic technology, private extension of the new technologies to such crops would in any case be discouraged by the high fixed cost of innovation. Creation of the engineered varieties involves substantial up-front investments to develop and protect enabling technologies, to identify useful genes, to engage in product advancement, and to negotiate the complicated and challenging regulatory and consumer acceptance issues associated with transgenic crops. Investments in applications of biotechnology for California's minor acreage crops may be hampered by the inability of innovators to capture sufficient revenue to justify their creation; the market may be too small given the costs involved and the rates of return required in the private sector. The smaller startups that have lower costs and more flexible response capacity are disappearing from many areas of agricultural biotech because, like nonprofits, they lack sufficient freedom to operate in the new research environment, and lack the resources to defend their IPR against infringement or legal challenges. Thus, if left to the private market, many applications of biotechnology to California crops are likely to be delayed or blocked altogether.

The private sector tends to be quite open about the narrowness of their applied research capabilities, and acknowledges that much of the basic research must be furnished or funded by the public sector. From the economic theory of basic research as a public good, the public-sector role is well accepted. For applications to crops that are not attractive to the private sector, the justification for public intervention is less clear. To the extent

that the major California crops are exported from the state, consumer benefits from lower prices or better quality are less relevant to California policy-makers; more of the benefits go to landowners and input-suppliers. Here, commodity groups have a clear informational advantage in identifying research needs, and a clear incentive advantage because they do not have to share research results with a third-party research firm. They need to find ways of continuing to collaborate on supporting public or collaborative industry research on their crops in a way that does not leave them shouldering the burden of developing useful technology without reaping the full benefits of the research. In a nutshell, the challenge is as follows: can the public and nonprofit research organizations continue their traditional collaborative functions, and can startups continue to play a vital role, given that many of the key enabling technologies are privatized and IPR trades are costly, risky, or even blockaded?

Intellectual Property and Freedom to Operate: An Illustrative Example

The varying effectiveness of plant protection strategies practiced by public- and private-sector interests has dramatically influenced the balance of power between these interests in agricultural biotechnology. Consider an example of how this situation could affect California rice growers. Assume public-sector breeders in California spent years developing a new rice variety, specifically suited for California. Support for this work included self-imposed producer assessments as well as state funds; the new seeds were distributed at roughly the cost of production.

Subsequently, a private agricultural biotechnology company acquired seeds of the variety and inserted genes for tolerance to their herbicides. The company would have invested substantial private resources developing the genetic engineering technologies needed to modify the rice variety, identifying appropriate gene(s) to confer the herbicide tolerance characteristic and discovering and registering the related herbicide.

The value of the herbicide tolerance would depend crucially on the productive potential of the elite germplasm into which the new gene was introduced. When the company offered the new,

herbicide-tolerant variety back to the original developers of the cultivar or to the broader agricultural community, who would reap the financial benefits from the improved variety? The answer would depend upon (PVPC) available prior to 1994, the original developer and its financial supporters would have no legal claim to share the profits from the new cultivar despite the fact that they successfully invested considerable resources in developing the original variety.

Additionally, if the seed company who bred the new herbicide-tolerant cultivar had no patent on the technology, and there was no protection available via hybridization, it would, after one season, find itself in competition with seeds grown by the first farmers to purchase and sow the seed, who could save their harvest for use or sale as rice seed. Most of the benefits then would accrue to farmers and consumers, rather than to the seed company.

Assume on the other hand, the seed company had protected its technology with a patent. It would be legally free to charge what the market would bear for its product and keep all the profits, if the developer had not acquired intellectual property protection of the original cultivar.

Farmers in less-developed and developed countries, who over the centuries have helped develop landrace ancestors of commercial varieties, may find themselves in a similar situation to the germplasm developer in this case. In the absence of effective recognition of “farmers’ rights,” they have no bargaining power that could force compensation for the use of their landraces or derived varieties.

If the original variety had received a PVPC after 1994, the situation might be different. The unanswered question of law is whether the new herbicide-tolerant variety infringes on the original PVPC, which was held by the public breeder. The issue is whether or not the herbicide-tolerant variety is, in the language of the act, “essentially derived” from the original variety. If it were, the developer of the transgenic variety would require permission from the original developer to improve the cultivar with the herbicide tolerance gene. Unfortunately, the

act does not offer a definition of “essentially derived” that could settle the question. To my knowledge, the extent of this legal protection has not been tested in court. Obviously, its resolution has powerful implications for owners of PVPC-protected cultivars.

If the original variety was protected by a utility patent, creation of the new cultivar would infringe that patent. That is, a license would be needed from the holders of the patent on the original cultivar in order to market the new variety. If the new cultivar were also patented, the developers of the original variety would similarly need a license to produce or use the genetically engineered version. Who pays and how much they pay for freedom to commercialize the transgenic seed depends upon the relative bargaining position, skills and experience of the parties, areas in which the larger private corporations, at present, tend to have a distinct advantage in most cases.

The above example is based on a real-world case. The public rice breeders who developed the elite germplasm for California did not protect it either with a utility patent or a PVPC. All the intellectual property rights are held by the breeder of the herbicide-tolerant germplasm. Rice growers today could have to pay a premium for the herbicide tolerant variety, but the private developer gets the complementary germplasm free. If the public breeding program in turn needs inputs from private science, they have little bargaining leverage unless they too have intellectual property rights. If they are to continue to create new varieties in the manner they have in the past, they will need to develop strategies to deal with this new reality.

Strategies for Obtaining the Freedom to Operate in the Agricultural Research that California Needs

In seeking strategies for achieving appropriate freedom to operate, it is first important to ensure that regulation of biotech research is appropriately designed and administered. Regulations are important for protecting health and safety and environmental quality. But regulation favors large, well-financed private conglomerates that thrive from the entry barriers they erect

against public and smaller private entities in the pharmaceutical sector. Public universities and some other nonprofit organizations are currently recognized by the public and private sectors as vital sources of relatively unbiased evaluation of regulations, and these sources should be utilized effectively.

For ideas on strategies to handle freedom to operate, a place to start is the set of solutions popular in the private sector. As discussed above, a popular private-sector solution is to avoid transaction problems by mergers or takeovers involving key IPR holders. It is unlikely that public institutions could solve their problems by merging with the private oligopolists who hold much of the relevant IPR.

Can the public/nonprofit research centers license their own IPR to pay for private IPR? This option has had considerable support by university policy-makers. Exclusive licenses are often more lucrative but it may not best serve the broader social interest toward which public institutions claim to be oriented. Even with exclusive licensing, universities will not make enough money from licensing their IPR to pay for the bulk of their biotech research. Moreover assertion of IPR by public institutions exacerbates their collective dilemma, as it privatizes what was previously a common pool of public resources, raising their transaction costs as they negotiate for each others' IPR.

Another approach to this problem is to exchange technology inputs under research licenses. The good news is that a research license allows use of proprietary technology in research; the bad news is that the licensor typically seeks to retain control of commercially interesting products, and is in a stronger bargaining position the more the research investment is committed by the licensee.³⁶²

Cross licensing, a popular option in the private sector, also raises real problems in the public sector. Cross-licenses are a

³⁶² Marshall, E., "NIH, DuPont Declare Truce in Mouse War." *Science* 281, (5381), 1998, 1261–1262.

favored mechanism for interactions among oligopolists. Exchanged as bargaining chips, they can help discourage other entrants. But in the public sector, a share of the value of the patent typically goes to the researcher. It will be hard to calculate properly such a fair share. The constraints on public licensing make their transaction costs even higher than those of the private sector.

Another strategy is to make a deal on market segmentation. The public or nonprofit organization might be able to negotiate an agreement whereby it gains access to technology from the private sector for uses quite distinct from those of interest to the IPR-holder. This is a promising alternative if the nonprofit has access to necessary information and negotiating skills, and is allowed to make such agreements with the private sector. One prototype is the cooperative research and development agreement (CRADA) that has had some success in enabling federal government to facilitate research on orphan drugs via public-private collaborations.^{363, 364} Another is the kind of arrangement AIDS drugs manufacturers are making to ensure supplies to poor consumers in some less developed countries, while charging higher prices elsewhere.³⁶⁵ To maintain political feasibility of such deals, the public must be made aware that such price discrimination can be beneficial to all parties, and if it stops, all can lose.

Finally, private support of public efforts can come directly from private firms. In some cases, private-sector entities are willing to fund public

³⁶³ Goodman, J., *The Story of Taxol: Nature and Politics in the Pursuit of an Anticancer Drug*, Cambridge, Cambridge University Press, 2001.

³⁶⁴ Day-Rubenstein, K. and K. O. Fuglie, "The CRADA Model for Public-private Research and Technology Transfer in Agriculture," Chapter 8, *Public-private Collaboration in Agricultural Research: New Institutional Arrangements and Economic Implications*, eds., K.O. Fuglie and D. E. Schimmelpfennig, Ames: Iowa State University Press, 2000.

³⁶⁵ Quaim, M., A.F. Krattiger and J. von Braun (eds.), *Agricultural Technology in Developing Countries: Towards Optimizing the Benefits for the Poor*, Dordrecht, Kluwer Academic Publishers, 2000.

research without claiming rights to outputs. This has been commonplace in engineering at many universities for many years, but is a more novel phenomenon in agriculture. One well-publicized Californian example is the involvement of a foundation funded by the multinational life science corporation, Novartis, in the support of plant biology research at the College of Natural Resources at the University of California, Berkeley.³⁶⁶ This support was conditioned on the right to be the first to negotiate the rights (as distinct from right of first refusal of licenses) to innovations arising out of research in plant biology that is supported by the donor, and the donor also has rights to appoint a minority of the board that directs research funded by the Foundation.³⁶⁷ But despite prominent expressions of concern,³⁶⁸ the conditions seem surprisingly mild, given the significant commitment (five years at \$5 million per year), and in particular much less stringent than appears in typical private-sector contracts with individual researchers. For example, in the agreement, the Novartis Foundation gets rights to first negotiation for only a portion of the patentable discoveries. Moreover, Novartis does not control the research done with its support, beyond the appointment of two members of a five-person committee who decide on allocation of the Foundation's funds to individual projects. Knowledgeable observers conjecture that a major portion of the return envisaged by Novartis consists of the benefits of intimate access to the intellectual resources of the Berkeley campus.

Another example is the donation by Monsanto Corporation of technology for transformation of corn (maize) by *Agrobacterium* technology to the University of California. As part of a divestiture of assets ordered by the U.S. Justice Department

as a condition for acquisition of DeKalb, the seed producer, Monsanto was required to relinquish one of two means of transformation it possessed. Rather than sell to a competitor, Monsanto, under extreme time pressure, was persuaded to give it to the University, and the University is free to license access to the technology to third parties. The details of this case illustrate the important point that prospective recipients must exercise flexibility and initiative to take advantage of such opportunities. (Incidentally, it is interesting that Monsanto was willing to make this donation soon after the Berkeley-Novartis agreement was announced. Apparently, Monsanto does not view Berkeley as "captured" by its competitor, Novartis.) The fact that private companies are willing to do these kinds of deals shows that the private sector values what the public sector has to offer, even in this new world of privatized research.

CONCLUSIONS

Over the years, the public sector in California, using mostly federal and state funds supplemented by support from some commodity groups, has been an important player in the development of new plant varieties. Classically bred varieties moved to the commercial field with no claims of legal protection. The revolution in biotechnology has opened up exciting new avenues for food and agricultural biotechnology. But the proliferation of proprietary claims on that technology heightens concerns about access by international and national agricultural research centers. The structure of these institutions places them at a disadvantage, in terms of resources and expertise, in the kind of bargaining over proprietary rights that occurs between for-profit corporations. For such institutions, professional assistance in handling IPR will be a continuing need.

It is important to realize that many of the problems of transactions in biotechnology IPR are shared by the large human health research complex. International agricultural research should try to inject their interests in the broader discussion of these issues, both in research leaders like the United States and the European Union, and in less-developed economies where law regarding IPR is being revised. Contractual innovations in

³⁶⁶ Rausser, G., "Public/Private Alliances," *AgBioForum* 2, (1), 1999, 5–10.

³⁶⁷ Mena, J. and R. Sanders, *Swiss Pharmaceutical Company Novartis Commits \$25 Million to Support Biotechnology Research at UC Berkeley*, University of California, Berkeley, Public Affairs News Release, 23, November, 1998, www.berkeley.edu/news/media/releases/98legacy/11-23-1998.html.

³⁶⁸ Press, E. and J. Washburn, "The Kept University," *Atlantic Monthly* 285, March (3), 2000, 39–54.

other areas of biotechnology transfer should be followed closely.³⁶⁹ Further research is needed on the dynamic implications of patents when technologies are cumulative.

Efforts should be made to turn the particular disadvantages of public agricultural research centers in conventional contracting into opportunities for success in alternative forms of technology transfer. One promising initiative is a proposal for sharing of access to intellectual property between public and non-profit research institutions for research on subsistence and “minor” crops, many of the latter being “major” for California.³⁷⁰ A related initiative to further investigate the possibility of development, for public and nonprofit use, substitutes for key “blocking” technologies held by the private sector. A third element is the support of an intellectual property “clearinghouse” to help researchers plan to maintain freedom to operate and trade in biotechnologies, as an alternative to integration and monopolization of the agricultural biotechnology research industry.^{371, 372}

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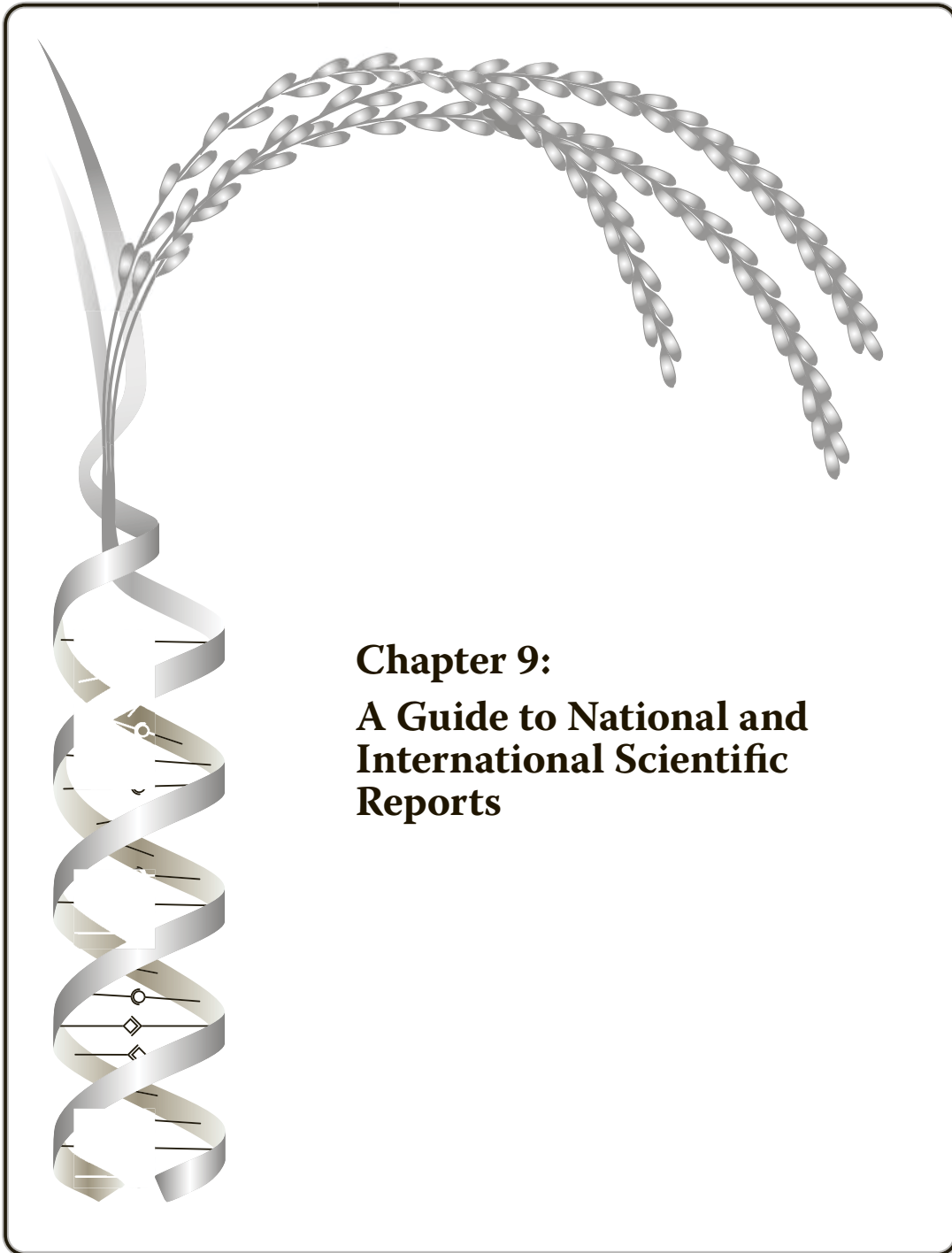
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³⁶⁹ See, for example, Lanjouw, J.O., “A Patent Proposal For Global Diseases,” *The Annual World Bank Conference on Development Economics*, eds., B. Pleskovic and N. Stern. Washington D.C., World Bank, Forthcoming, 2001.

³⁷⁰ Graff, Gregory, “Intellectual Property Sharing for Public-Foundations, 2/22/02.

³⁷¹ Graff, G. and D. Zilberman, “Towards an Intellectual Property Clearinghouse for Agricultural Biotechnology,” *IP Strategy Today* No. 3-2001, 1-11.

³⁷² Graff, G, A. Bennett, B. Wright and D. Zilberman, “A Summary of Workshop Proceedings,” *Proceedings of a meeting on Intellectual Property Clearinghouse Mechanisms for Agriculture*, held at University of California, Berkeley, February 16, 2001, Online at <http://www.CNR.Berkeley.EDU/csrtd/technology/ipcmech/Summary-Berkeley-2-16-2001-AgBio-IP-Clearinghouse-Workshop.pdf>.



**Chapter 9:
A Guide to National and
International Scientific
Reports**

Chapter 9: A Guide to National and International Scientific Reports

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In the last two years, there have been many national and international scientific panel reviews of food biotechnology and other aspects of the subject. Summaries of these recent reports are being included in this review for those who want to obtain more detailed information about the scientific communities' views on food biotechnology. The full reports are readily available for download on the Internet.

OVERVIEW

Overview of Biotechnology, Institute of Food Technologists (IFT). *Food Technology*, Vol. 54, No. 8: 1-14, August 2000.

<http://www.ift.org/govtrelations/biotech/>

The report published in three issues of *Food Technology* consists of four sections: Introduction, Safety, Labeling, and Benefits and Concerns. The focus of these reports is on rDNA biotechnology-derived foods, food ingredients, and animal feed of plant origin and on the use of rDNA biotechnology-derived microorganisms such as yeasts and enzymes in food production. Transgenic animals resulting from the application of rDNA biotechnology techniques to animal production was not addressed. The introduction presents background information to help readers understand rDNA biotechnology-derived foods, and federal regulation and oversight of rDNA biotechnology. The point was made that, in the view of many knowledgeable scientists, rDNA biotechnology-derived foods are the latest major step in a 10,000-year process of genetic improvement of food. Biotechnology in the broadest sense is, in fact, not a discrete technology. It refers to a group of useful enabling techniques, including but not limited to genetic modification, that have wide application in research and commerce. During the past several decades, such techniques have become so integrated into the practice of plant breeding and microbiology and so commingled with conventional techniques as to blur distinctions between "old" and "new". A useful

working definition of biotechnology that is used by the U.S. governmental agencies is the application of biological systems and organisms to the production of useful goods and services. In developing these state-of-the-science reports, it is IFT's intent to promote a meaningful public discussion of the subject that is based on sound science.

Benefits and Concerns Associated with Recombinant DNA Biotechnology-Derived Foods. Benefits and Concerns Panel, Stanford A. Miller, Anthony Artuso, Dennis Avery, Roger Beachy, Peter R. Day, Owen R. Fennema, Ralph Hardy, Peter L. Keeling, Todd R. Klaenhammer, Martina McGloughlin, and Anne K. Vidaver, IFT Expert Report on Biotechnology and Foods, *Food Technology*, Vol. 54, No. 10: 37-56, October 2000.

<http://ift.org/govtrelations/biotech/>

This report considers in detail numerous specific benefits of biotechnology. Concerns addressed include economic and access-related concerns, research incentives, environmental concerns, monitoring, allergenicity, antibiotic resistance transfer, and naturally occurring toxicants. The Benefits and Concerns Panel concluded that further development and use of rDNA biotechnology-derived foods provides a number of benefits. Based on its evaluation of currently available scientific information, the following benefits and concerns were presented by the Panel:

- A more abundant and economical food supply in the world;
- Continued improvements in nutritional quality, including foods of unique composition for populations whose diets lack essential nutrients;
- Fresh fruits and vegetables with improved shelf life;
- Foods with reduced allergenicity;
- The development of functional foods, vaccines, and similar products may provide health and medical benefits;

- Further improvements in production agriculture;
- The conversion of non-productive toxic soils in developing countries to productive arable land; and
- More environmentally friendly agriculture, through improved pesticide usage, less hazardous animal wastes, improved utilization of land, and reduced need for ecologically sensitive lands such as rain forests.

With regard to concerns, the Panel reached the following conclusions:

- New rDNA biotechnology-derived foods and food products do not inherently present any more serious environmental concerns and unintended toxic properties than those already presented by conventional breeding practices, which have an impressive safety record;
- Appropriate testing by technology developers, producers, and processors, regulatory agencies, and others should be continued for new foods and food products derived from all technologies, including rDNA biotechnology-derived foods; and
- Programs should be developed to provide the benefits of safe and economical rDNA biotechnology-derived food products worldwide, including in less-developed countries.

Genetically Engineered Foods 2001: A Consumer Guide to What's in Store, Susan Henry.
www.nysaes.cornell.edu/comm/gmo/ and
www.geo-pie.cornell.edu

A collaborative effort by Cornell University and Cornell Cooperative Extension to identify a variety of issues about agricultural biotechnology, offer different viewpoints on each and provide links for further information. There are sections on Agricultural Biotechnology:

- Questions and Answers, Tools & Methods, Applications, The Debate, Glossary & References. It discusses what GE foods are in the market, what traits have been engineered into plants, and the risks and benefits of genetic engineering. Some of the conclusions are as follows:

- Recent estimates suggest that more than 60% of food products in U.S. markets contain at least a small quantity of some crop that has been genetically modified;
- There have been 12 genetically engineered plant species that have been approved for commercial production in the U.S. with traits for insecticide resistance, herbicide resistance, virus resistance, altered oil content, delayed fruit ripening, and pollen control;
- Food plants are known to produce a wide array of chemicals, and although the levels of many of the more toxic ones have been reduced in the process of domestication, many of these natural toxins are still present;
- Because of the potential for bacteria picking up an antibiotic resistance gene, the use of resistance genes as markers is being phased out by developers;
- In general, there has been a modest decline in the quantity of pesticides applied to corn, cotton, and soybeans since 1995; and
- Many experts feel that the likelihood of GE-induced allergies is very small, if not impossible, to predict the allergenicity of proteins in any new food including new conventional foods.

HEALTH AND SAFETY

Human Food Safety Evaluation of rDNA Biotechnology-Derived Foods - Human Food Safety Panel, Dallas Hoover, Bruce M. Chassy, Richard L. Hall, Harry J. Klee, John B. Luchansky, Henry I. Miller, Ian Munro, Ronald Weiss, Susan L. Hefle, and Calvin O. Qualset, IFT Expert Report on Biotechnology and Foods, Food Technology, Vol. 54, No. 9:53-61, September 2000.
<http://ift.org/govtrelations/biotech/>

This section discusses issues relevant to safety evaluation of rDNA biotechnology-derived foods, including the concept of substantial equivalence, introduced genetic material and gene products, unintended effects, allergenicity, and products without conventional counter parts. The international scientific consensus regarding the safety of rDNA biotechnology-derived foods is also discussed. Based on its evaluation of the

available scientific evidence, the Human Food Safety Panel reached the following conclusions:

- Biotechnology has a long history of use in food production and represents a continuum of old traditional breeding techniques and the latest techniques based on molecular modification of genetic material. The newer rDNA biotechnology techniques offer the potential to rapidly and precisely improve the quantity and quality of food available.
- Crops modified by modern molecular and cellular methods pose risks no different from those modified by earlier genetic methods for similar traits. Molecular methods are more specific and users of these methods will be more certain about the traits they introduce into plants.
- The evaluation of foods, food ingredients, and animal feed developed with newer rDNA technologies do not require a fundamental change in established principles of food safety nor do they require a different standard of safety, even though, more information and a higher standard of safety are being required.
- The science that underlies rDNA biotechnology does not support more stringent safety standards than those that apply to conventional foods.
- The use of genetic engineering significantly broadens the scope of possible sources of genetic changes in foods, but this does not inherently lead to foods that are less safe than those developed by conventional techniques. By virtue of their greater precision, such products can be expected to be better characterized, leading to more predictability and a more reliable safety assessment process.

Food Safety Assessment, Leon G. Higley, Blair D. Siegfried, John E. Foster, Steve Taylor, Georgianna Whipple, Ron J. Roeber, and Donald J. Lee, University of Nebraska Ag Biosafety Education Center Website.
<http://agbiosafety.unl.edu/about.htm>

In recent years, the increased development of genetically modified foods and agricultural biotechnology has sparked public interest. AgBiosafety is a website created by the University of Nebraska-Lincoln, dedicated to addressing current issues in crop biotechnology and food safety. Goals are:

- To offer a comprehensive, up-to-date source of information on the current issues in biotechnology and food safety;
- To provide consumers, educators, and policy makers with an easily accessible source of data and facts related to crop biotechnology;
- To provide topical articles on current issues in biotechnology and food safety; and
- To provide educational resources and curricula on crop biotechnology for both consumers and educators.

Database of Safety Information provides complete descriptions for each of the crops that have received regulatory approval in Canada, the United States, and elsewhere. For each product, there is detailed information on how it was produced and what concerns were addressed during the risk assessments for environmental and food safety. There is also a range of product-specific background information, linkages to regulatory decision summaries, and information on which countries have granted product approval.

Global Status of Approved Genetically Modified Plants offers information based on data obtained from our global database of genetically modified plants. The database includes not only plants produced using recombinant DNA techniques (e.g., genetically engineered or transgenic plants), but also plants with novel traits that may have been produced using more traditional methods, such as accelerated mutagenesis or plant breeding. These latter plants are only regulated in Canada.

Crops and Traits provides a listing of novel traits by crop species. In each case, the number of events with a particular trait is also provided.

Genetic Elements

A regulatory approvals table provides a summary of the regulatory approval status for each genetically modified crop.

The Education Center at <http://www.agbio.safety.unl.edu/education.htm> has educational materials with the goal of teaching the science of crop biotechnology. The Education Center also has case studies, interactive learning modules, and self-assessment instruments for use in both college and high school level classrooms.

Environment Safety Assessment Module provides an environmental risk assessment module that was developed to provide background information on the approaches used by regulatory agencies when evaluating the environmental safety of genetically engineered and other novel crops. The concepts of risk assessment as discussed here do not reflect any one country's regulatory approach, but rather have been modeled after international consensus documents such as those produced by the Organization for Economic Cooperation and Development (OECD), the World Health Organization (WHO), and the Food and Agriculture Organization (FAO) of the United Nations.

This module has been organized as a series of eight topic areas. The first three topic areas (Concepts and Principles, Modification Method, and Molecular Genetic Characterization) either closely parallel or exactly duplicate topics that are also addressed in the module on food safety assessment. In the case of the latter two topics, these are issues that are common to both types of safety assessment. Links to each chapter (topic) are accessible from the sidebar, and from the listing below:

- Concepts and Principles provides a framework of internationally accepted approaches to assessing environmental safety;
- Modification Method - relevance of the method of production in determining subsequent information requirements;

- Molecular Genetic Characterization shows the significance of characterizing the inserted DNA, its genetic stability (inheritance), and expressed proteins;
- Gene Transfer to Related Plants discusses the risks associated with gene flow via outcrossing to sexually compatible plants in either managed or unmanaged ecosystems;
- Gene Transfer to Unrelated Organisms - the potential for the non-sexual exchange of genetic material between organisms belonging to the same, or different species;
- Weediness potential for a genetically modified plant to successfully colonize a managed and/or an unmanaged ecosystem. Secondary & Non-Target Adverse Effects - unintended consequences of the environmental release of a transgenic plant, particularly as this may impact on existing agricultural practices and the agroecosystem; and
- Insect Resistance Management explains the requirement for mandatory implementation of insect resistance management (IRM) plans designed to mitigate the development of *Bt* resistant insect pest populations.

Food Safety Assessment module was developed to provide background information on the approaches used by regulatory agencies when evaluating the safety of genetically modified and other novel foods. Without exception, all of the crop biotechnology products that have received regulatory approval for use in food have been evaluated using approaches and criteria consistent with those described in this document.

This module has been organized as a series of seven topic areas that closely parallel the specific safety issues that should be considered when evaluating a new food.

- Concepts and Principles provides a framework of internationally accepted approaches to assessing food safety;
- Host and Donor Organisms: importance of background information on both the host plant and the donor organism (source of genes) in structuring the safety assessment;

- **Modification Method:** relevance of the method of production in determining subsequent information requirements;
- **Molecular Genetic Characterization:** significance of characterizing the inserted DNA, its genetic stability (inheritance), and expressed proteins;
- **Nutritional Data** analyses the nutritional composition and nutrient bioavailability;
- **Toxicity:** toxicological analysis of novel proteins and unintended effects of the genetic modification; and
- **Allergenicity:** food allergen concerns related to novel foods.

The Safety of GM Foods module provides information on the regulation of livestock feeds containing products derived from genetically modified (GM) crops in Canada and the United States, and on the studies that have been carried out to assess the safety of these novel feeds. The topics covered in this module include:

The regulatory and safety assessment process; the nature of GM crops currently used as livestock feed components; the safety of new protein introduced into GM crops; comparing the nutritional composition and efficacy of novel and conventional livestock feeds; the metabolic fate of ingested protein and DNA, including the fate of novel proteins; and DNA introduced through genetic engineering techniques.

Protein and DNA contained in foods and feeds, whether obtained from non-GM or GM crops, are typically degraded upon consumption by the normal digestive processes. For those commercially available GM crops that are components of livestock feeds, there is no evidence of significantly altered nutritional composition, deleterious effects, or the occurrence of transgenic DNA or proteins in subsequent foods of animal origin. These data, together with the history of safe usage of the transgenic proteins in agriculture and/or their similarity to already occurring constituents, provide a substantial assurance of safety.

Safety Aspects of Genetically Modified Foods of Plant Origin, Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology, World Health Organization, Geneva, Switzerland, June 2000, 37 pages.

A total of 27 experts, including authors of this discussion paper, participated in this report which provides scientific support in relation to the safety and nutritional features of foods derived from biotechnologies on the basis of available scientific data, reviews existing strategies for the safety and nutritional assessment of foods derived from biotechnology, and makes recommendations on further research needs and priorities for the evaluation of safety and nutritional aspects of foods derived from biotechnology. The conclusions of the consultation are as follows:

- They agreed that the safety assessment of genetically modified foods requires an integrated and stepwise, case-by-case approach focusing on the determination of similarities and differences between the genetically modified food and its conventional counterparts.
- They were of the view that there were presently no alternative strategies that would provide a better assurance of safety for genetically modified foods than the appropriate use of the concept of substantial equivalence.
- They agreed that the safety assessment of genetically modified foods requires methods to detect and evaluate the impact of unintended effects even though the occurrence of unintended effects are not unique to the application of recombinant DNA techniques but are also a general phenomenon in conventional breeding.
- They noted that very little is known about the potential long-term effects of any foods, and they acknowledged that, for genetically modified foods, the premarketing safety assessment already gives assurance that the food is as safe as its conventional counterpart.
- They recognized that genetically modified foods with intentional nutritional effects may provide improved products for developed and developing countries. It is important to determine alterations in

nutrient content and bioavailability and their stability with time, processing and storage, as well as to monitor changes in dietary patterns of consumers.

- They agreed that, if a genetically modified food contains the product of a gene from a source with known allergenic effects, the gene product should be assumed to be allergenic unless proven otherwise. The transfer of genes from commonly allergenic foods should be discouraged.
- They considered horizontal gene transfer from plants and plant products consumed as food to gut microorganisms or human cells as a rare possibility, but noted that it cannot be completely discounted.

**Report 10 by the American Medical Association
American Medical Association: Genetically
Modified Foods, January 2000.**

<http://www.ama-assn.org/ama/pub/article/2036-3604.html>

This report presents a review of the technology used to produce transgenic crops and an examination of the issues relevant to the utilization of transgenic crops and genetically modified foods, including the current regulatory framework, possible human health effects, potential environmental impacts, and other consumer-related issues. More than 40 transgenic crop varieties have been cleared through the federal review process with enhanced agronomic and/or nutritional characteristics or one or more features of pest protection (insect and viruses) and tolerance to herbicides. The most widely used transgenic pest-protected plants express insecticidal proteins derived from the bacterium *Bacillus thuringiensis* (*Bt*). Crops and foods produced using recombinant DNA techniques have been available for fewer than 10 years and no long-term effects have been detected to date. These foods are substantially equivalent to their conventional counterparts. Genetic engineering is capable of introducing allergens into recipient plants, but the overall risks of introducing an allergen into the food supply are believed to be similar to or less than that associated with conventional breeding methods. The risk of horizontal gene transfer from plants to environmental bacteria

or from plant products consumed as food to gut microorganisms or human cells is generally acknowledged to be negligible, but one that cannot be completely discounted. Pest-resistance due to exposure to *Bt* containing plants has not occurred to date, and harmful effects on non-target organisms, which have been detected in the laboratory, have not been observed in the field. Nevertheless, these and other possible environmental effects remain areas of concern. It was concluded that federal regulatory oversight of agricultural biotechnology should be science based. Methods to assure the safety of foods derived from genetically modified crops should continue to be refined and improved. Although no untoward effects have been detected, the use of antibiotic markers that encode resistance to clinically important antibiotics should be avoided if possible. Genetic modification of plants could potentially lead to detrimental consequences to the environment. Therefore, a broad-based plan to study environmental issues should be instituted. There is no scientific justification for special labeling of genetically modified foods, as a class, and voluntary labeling is without value unless it is accompanied by focused consumer education. Government, industry, and the scientific and medical communities have a responsibility to educate the public and improve the availability of unbiased information on genetically modified crops and research activities.

**Biotechnology and Food, Prepared for the American
Council on Science and Health, Ruth Kava, Project
Coordinator for a panel of 17 expert contributors,
September 2000.**

<http://www.acsh.org>

Conclusions: Modern biotechnology is being used in agriculture and food production to provide more, better, and safer products. The extent to which it will be fully utilized for the benefit of consumers depends on support for innovation and improvement of farming and food production, on the one hand, and on support for scientifically sound regulatory policies that protect against tangible food safety risks, on the other. This is a delicate balance. Medical and human health biotechnology, using similar genetic techniques, is well accepted by the public and professional

communities as a safe and effective means to provide more and better treatments. Because agricultural biotechnology is younger and some critics remain wary, new food products will appear gradually in the marketplace over the next few years. However, with the continuing accumulation of evidence of safety and efficiency, and the complete absence of any evidence of harm to the public or the environment, more and more consumers are becoming as comfortable with agricultural biotechnology as they are with medical biotechnology. With the research pipeline filled, consumers and farmers can expect a wide variety of new products in the not too distant future.

ENVIRONMENT

Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation, Frederic L. Gould (Chair), David A. Andow, Bernd Blossey, Ignacio Chapela, Norman C. Ellstrand, Nicholas Jordan, Kendall R. Lamkey, Brian A. Larkins, Deborah K. Letourneau, Alan G. McHughen, Ronald L. Phillips, Baul B. Thompson, Committee on Environmental Impacts Associated with Commercialization of Transgenic Plants, National Research Council, National Academy Press, February 2002.
<http://books.nap.edu/books/0309082633/html/1.html>

The task of the committee was to evaluate the scientific premises and assumptions underpinning the environmental regulation and oversight of transgenic plants by USDA-APHIS. The committee reported on three general areas as follows:

Environmental Effects of Agricultural Practices, Novel Genetic Material, and the Processes Used in Plant Improvement

- Small and large genetic changes have had substantial environmental consequences;
- The consequences of biological novelty depend strongly on the specific environment, including the genomic, physical, and biological environments into which they are introduced;

- The significance of the consequences of biological novelty depend on societal values;
- Introduction of biological novelty can have unintended and unpredicted effects on the recipient community and ecosystem;
- There is no strict dichotomy between the possibility of environmental hazard associated with the releases of cultivated plants with novel traits and the introduction of nonindigenous plant species;
- Agreed with previous NRC report that both transgenic and conventional approaches for adding genetic variation to crops can cause changes in the plant genome that result in unintended effects on crop traits;
- Transgenic process presents no new categories of risk compared to conventional methods of crop improvement, but that specific traits introduced by both applications can pose unique risks;
- The scientific justification for regulation of transgenic plants is not dependent on historically set precedents for not regulating conventionally modified plants; and
- It should be possible to relatively quickly screen modified plants for potential environmental risk and then conduct detailed tests for potential risk.

Risk Analysis and the Regulation of Transgenic Plants: Scientific Assumptions and Premises

- Risk analysis of transgenic plants must continue to fulfill two distinct roles: (1) technical support for regulatory decision-making and (2) establishment and maintenance of regulatory legitimacy;
- Risks must be assessed on a case-by-case basis with consideration for the organism, trait and environment; and
- In any attempt to mitigate environmental risk, there is a need to be mindful of the fact that avoiding one risk can sometimes inadvertently cause another greater risk.

Analysis of the APHIS Regulatory Process

- APHIS and other regulatory agencies charged with assessing the safety of transgenic plants face a daunting task;
- APHIS regulatory system has improved substantially since it was initiated;

- The development of a notification process that utilizes ecologically based performance standards was an important step in effectively streamlining the field-testing process;
- APHIS currently has the authority to base regulatory scrutiny on potential plant pest status, regardless of the process of derivation;
- The notification process is conceptually appropriate, but that there is a need to reexamine which transgenic plants should be tested and commercialized through the notification process;
- The APHIS process should be made significantly more transparent and rigorous by enhanced scientific peer review, solicitation of public input, documents with more explicit presentation of data, methods, analysis and interpretations;
- APHIS should not use the term “no evidence” and general “weediness” characteristics in its environmental assessments;
- For pesticidal plants, APHIS should either increase the rigor of assessments of resistance risk and non-target impacts or completely defer to the EPA which also assesses these risks;
- That the extent of confidential business information in registrant documents sent to APHIS hampers internal review and transparency of the decision-making process; and
- APHIS should involve more groups of interested and affected parties in the risk analysis process while maintaining a scientific basis for decisions.

Postcommercialization Testing and Monitoring

- There are several compelling arguments for validation-testing and ecological monitoring after commercialization of transgenic plants;
- Postcommercialization validation testing should be used to assess the adequacy of precommercialization environmental testing;
- Two different types of general ecological monitoring be used to assess unanticipated

or long-term, incremental environmental impacts of transgenic crops;

- The U.S. does not have in place a system for environmental monitoring of agricultural and natural ecosystems that would allow for adequate assessment of the status and trends of the nation’s biological resources;
- That a body independent of APHIS be charged with the development of an indicator-monitoring program; and
- That a process be developed that allows clear regulatory responses to findings from environmental monitoring.

Transgenic Crops: An Environmental Assessment, David E. Ervin, Sandra S. Batie, Rich Welsh, Chantal L. Carpentier, Jacqueline I. Fern, Nessa J. Richman, Mary A. Schulz, Henry A. Wallace Center for Agricultural & Environmental Policy at Winrock International, November 2000, 81 pages.
http://winrock.org/what/wallace_center.asp

Reviews and assesses scientific and policy literature on the positive and negative environmental impacts of genetically engineered (transgenic) crops. Examines extent of current usage, biosafety regulation, and business aspects, with focus on the United States and European Union. The environmental effects (Chapter 1) of a transgenic crop depend on the characteristics of the organism, the environmental system in which the crop is placed, and the skill with which it is managed. In short, whether a transgenic crop will benefit or adversely affect the environment depends on the nature of the crop, where it is used and how it is used. Hence, we may expect a range of environmental effects, some positive and some negative. The environmental impacts are shaped also by current biosafety regulation (Chapter 2). Unfortunately, the politics for managing the varying environmental impacts are hindered by the relatively small core of scientific data with which to anticipate and develop appropriate control measures. Many commentators have come to believe that the existing regulatory framework is inadequate. In fact, a recent National Research Council report has recommended a number of actions to strengthen, the regulatory process for genetically modified pest-protected plants.

Two policy changes involving intellectual property rights (IPR) have played key roles in propelling the agricultural biotechnology (Chapter 3) revolution and raising environmental issues. First, a narrow 1980 U.S. Supreme Court decision provided the legal basis for granting intellectual property protection for living organisms, in the form of invention patents. Second, under the 1980 Bayh-Dole Act, public universities and other institutions receiving federal research funds also can patent biotechnology inventions and license them for revenues. The IPR changes likely have influenced the trajectory of biotechnology development, encouraging investment in products with the greatest profit potential. Changes may contribute also to a more concentrated industry structure, resulting in less competition and product innovation. Market forces may limit or expand transgenic crop plantings' environmental benefits and risks. With governments not able to reassure a growing portion of the public about foods made with transgenic ingredients, especially in the EU countries, market forces may play a critical role.

With varying IPR regimens around the world and the uncertainty of implementing the Trade Related Intellectual Property (TRIPS) agreement after the 1999 Seattle WTO Ministerial Meeting, further uncertainty is added. The TRIPS agreement, among other provisions, defines the process through which countries can adopt IPR regimens that facilitate trade in agricultural biotechnology. Given the unsettled state of affairs, the diffusion and trade in transgenic crop seeds and products may proceed erratically for some time.

Conclusion (Chapter 4): Given the potential risks of transgenic crops to the environment, and to the biotechnology industry as a whole, a cautious approach to the use and dissemination of transgenic crops is appropriate. There are two key elements to this cautious approach:

- Increase investment in public research and development for agricultural biotechnology to ensure that the neglected environmental aspects of transgenic crops receive adequate attention, and to build a credible scientific knowledge base, including a comprehensive monitoring system, by which to evaluate

these crops and their environmental impacts; and

- Develop appropriate regulatory frameworks for transgenic crops, and reform the institutions and regimens, such as IPR, that control their development and diffusion. The report also contains a glossary of terms, list of transgenic crops in the U.S., and list of information sources.

REGULATION

Genetically Modified Pest-Protected Plants: Science and Regulation, National Research Council, National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, Perry Adkisson, Stanley Abramson, Stephen Baenziger, Fred Betz, James C. Carrington, Rebecca J. Goldberg, Fred Gould, Ernest Hodgson, Tobi Jones, Morris Levin, Erik Lichtenberg, and Allison Snow, National Academy Press, Washington, D.C., 2000, 261 pages.
<http://nap.edu>

The report is composed of four chapters and an executive summary.

Chapter 1 is an introductory chapter that discusses issues, which led to the initiation of the study, current EPA, USDA, and FDA policies, and the role of the report.

Chapter 2 deals with the potential environmental and human health impacts of pest-protected plants with risks and benefits being among the issues discussed.

Chapter 3 provides several case studies related to the commercial production of transgenic pest-protected crops, analyses the 1994 and 1997 rules proposed by EPA for the regulation of plant-pesticides, and identifies several research needs.

Chapter 4 provides an overview of the current regulation on biotechnology by EPA, FDA, and USDA and provides recommendations that the committee believes will improve the process.

This report provides advice to researchers, developers, and regulatory agencies involved in reviewing the science surrounding the regulation of genetically modified, pest-protected crops. The report addresses only one aspect of the ongoing revolution in the life sciences and agriculture,

and it is careful to point out where more research and scientific information is needed to answer remaining questions. The report reviewed three general principles: Potential Environmental and Human Health Implications of Pest-Protected Plants; Crossroads of Science and Oversight; and Strengths and Weaknesses of the Current Regulatory Framework. The committee found that priority should be given to the development of improved methods for identifying potential allergens in pest-protected plants, specifically the development of tests with human immune-system endpoints and of more reliable animal models. The report recommended the following:

- Assess and enhance data on the baseline concentrations of plant compounds of potential dietary or other toxicological concern, and determine how concentrations of these compounds may vary depending on the genetic background of the plant and environmental conditions;
- Examining whether long-term feeding of transgenic pest-protected plants to animals whose natural diets consist of quantities and type of plant material being tested; and
- Encourage the EPA, FDA, and USDA to collaborate on the establishment of a database for natural plant compounds of potential dietary or other toxicological concern. The committee was not aware of any evidence that foods on the market were unsafe to eat as a result of genetic modification.

LABELING

Labeling of rDNA Biotechnology-Derived Foods, Labeling Panel, John E. Vanderveen, John W. Bode, Christine M. Bruhn, Elizabeth Campbell, Susan K. Harlander, Gerald Nelson, and Steve Taylor, IFT Expert Report on Biotechnology and Foods, Food Technology, Vol. 54, No. 9: 62-74, September 2000. <http://ift.org/govtrelations/biotech/>

This report provides an overview of the relevant U.S. food labeling requirements, including constitutional limitations on the government's authority to regulate food labeling and specific case studies relevant to labeling rDNA biotechnology-derived foods. The section

also discusses U.S. and international labeling policies for rDNA biotechnology-derived foods and the impact of labeling distinctions on food distributions systems. Consumer perceptions of various label statements from the U.S. and other countries are also discussed. The information on food labels is highly regarded by consumers and is considered one of the most reliable sources of information. The Labeling Panel drew the following conclusions:

- The regulatory system requires disclosure of any significant difference in the characteristics of an rDNA biotechnology-derived food. In addition, voluntary label statements must be substantiated and not misleading, either overtly, by implication, or my omission;
- Mandatory label disclosure requirements may not reach beyond addressing material facts about a food. Absent significant differences, the fact that a food is rDNA biotechnology-derived is not a material fact;
- Voluntary labels have been used to establish markets for niche categories of foods desired by consumers;
- Labeling initiatives for rDNA biotechnology-derived foods may have substantial effects on the production, distribution and cost of food to consumers; and
- Terminology used in labeling should convey information to the public in an understandable, accurate, and non-misleading manner.

Information Systems for Biotechnology: A National Resource in Agbiotech Information, a program administered by the USDA's Cooperative State Research, Education and Extension Service and is a part of the National Biological Impact Assessment Program. <http://www.nbiap.vt.edu>

This website features documents, searchable databases pertaining to the development, testing and regulatory review of genetically modified plants, animals, and microorganisms within the U.S. and abroad. There are databases of U.S. and International Field Tests of GMOs and Lists of U.S. and International Commercialized Crops. It also provides links to Agbiotech websites.

Applications of Biotechnology to Crops: Benefits and Risks, CAST Issue Paper No. 12, Gabrielle J. Persley, and James N. Siedow, Reviewers: Michael Gasson and Calvin O. Qualset, Council for Agricultural Science and Technology, December 1999, 7 pages.

<http://cast.science.org>

Their definition of biotechnology is any technique that uses living organisms or parts thereof to make or modify a product or improve plants, animals, or microorganisms for specific uses. The application of DNA technology to facilitate genetic exchange in crops has several advantages over traditional breeding methods. It is more precise because only a single or at most, a few specific genes are being transferred to the recipient. The application of agricultural biotechnology can improve the quality of life by increasing productivity of crops, primarily by reducing costs of production and by decreasing the needs for inputs of pesticides, expanding the range of environments that plants can be grown in, better crop rotations to conserve natural resources, provide more nutritious products that keep longer in storage and transport, and continue low cost food supplies to consumers. In assessing the risks in the use of modern biotechnology, it is important to distinguish between “technology-inherent risks” and “technology-transcending risks”. Technology-inherent risks are any risks associated with food safety and behavior of a biotechnology-based product in the environment. Technology-transcending risks emanate from the political and social context in which technology is used and how these uses may benefit and/or harm the interest of different groups in society. Regulatory trends to govern the safe use of biotechnology to date, include undertaking scientifically based, case-by-case, hazard identification and risk assessments. The health effects of foods grown from genetically modified crop varieties depends on the specific content of the food itself and may have either potentially beneficial or occasional harmful effects on human health. Among the potential ecological risks are increased weediness, development of insect resistance to the *Bt* gene, and risks to non-target species. In conclusion, they felt that governments and other responsible parties should be informed about the nature of new crop types and new

crop varieties, about unity of life processes in all organisms, and about the risks and benefits of agricultural biotechnology in their own country and internationally.

ECONOMICS

Economic Issues in Agricultural Biotechnology, Robbin Shoemaker, Joy Harwood, Kelly Day-Rubenstein, Terri Dunahay, Paul Heisey, Linwood Hoffman, Cassandra Klotz-Ingram, William Lin, Lorraine Mitchell, William McBride, and Jorge Fernandez-Cornejo, ERS Agricultural Information Bulletin No. 762, March 2001, 64 pages.

<http://ers.usda.gov/publications/aim762/>

This report identified several key areas—agricultural research policy, production and marketing, consumer issues, environmental safety, and future world food demand—where agricultural biotechnology is dramatically changing the public policy agenda. The current situation is extremely fluid, with the day’s headlines, rather than the underlying issues, often dominating discussion. Public policy is made more difficult by the fact that, in essence, “agricultural biotechnology” encompasses multiple policy objectives targeted by multiple policy instruments. For example, public research funding, the intellectual property regime, and antitrust policy particularly influence the speed and direction of agricultural research. Intellectual property policy and antitrust policy as well as regulation, including the system of grades and standards for agricultural commodities, affect agricultural production and marketing. Regulation, along with public collection and dissemination of information on risk, plays a role in food safety and environmental issues. Public policy becomes even more complicated when international jurisdictions are involved with the exports of biotech crops to traditional markets. Markets will determine the future of agricultural biotechnology, but it is important to remember that these markets will always function in the context of policy issues discussed in this report.

Economics of Food Labeling, Elise Golan, Fred Kuchler and Lorraine Mitchel, ERS Agricultural Information Bulletin No. 793. December 2000.
<http://ers.usda.gov/publications/aim793/>

In this report, they trace the economic theory behind food labeling and present three case studies in which the government has intervened in labeling decisions, and two examples in which government intervention has been proposed (country of origin and biotech). They also examined how different types of benefit-cost calculations influenced the information supplied by private firms, the information required by governments, and the role of third party entities in standardizing and certifying the veracity of the information. Federal intervention in food labeling is often proposed with the aim of achieving a social goal such as improving human health and safety, mitigating environmental hazards, averting international trade disputes, or supporting domestic agricultural and food manufacturing industries. They conclude that labeling may be an appropriate policy tool in the following circumstances:

- Consumer preferences differ;
- Information is clear and concise;
- Information on product use enhances safety;
- Costs and benefits of consumption are borne by the consumer;
- Standards, testing, certification, and enforcement services can be established; and
- No political consensus on regulation exists.

SOCIAL AND PUBLIC POLICY ISSUES

Agricultural Biotechnology: The Public Policy Challenges, Edited by Andrew M. Isserman, Sage Periodicals Press, Thousand Oaks, CA, American Behavioral Scientist Vol. 44: 3, November 2000, 115 pages.
<http://sagepub.com>

Mobilizing a University for Important Social Science Research Biotechnology at the University of Illinois. Complex societal issues, such as those raised by agricultural biotechnology and genetically modified food, call for prompt, large-

scale multidisciplinary research. Universities encounter powerful institutional impediments when trying to respond. These articles describe a successful experiment designed to overcome those impediments and build university research capacity. Twenty-five faculty members from four colleges joined together to learn more about biotechnology. Within one year they produced 20 useful journal articles to help themselves and others understand the emerging issues, possibilities, and policy options.

Agricultural Biotechnology for Developing Countries Prospects and Policies, Mary Arends-Kuenning and Flora Makundi, University of Illinois at Urbana-Champaign.

Will the biotechnology revolution improve the living standards of poor rural farmers in developing countries? The Green Revolution showed that the economic and social structure in a society play a larger role in determining how innovations affect people than the scientific content of the innovations. Social and economic structure within developing countries and within the international community will determine what crops are enhanced using biotechnology, which traits of the crops are altered, and how the new seeds and plantlets will be distributed. The fact that the private sector is taking the lead in biotechnology rather than public-sector institutions has important implications for developing countries. Crops with high public benefits will not be developed by the private sector if they are not profitable. The public sector and nonprofit sector, in collaboration with the private sector, have important roles to play to ensure that benefits of biotechnology are available to the poor in developing countries.

U.S. Regulatory Oversight of Agricultural and Food-Related Biotechnology, Donald L. Uchtmann and Gerald C. Nelson, University of Illinois at Urbana-Champaign.

Genetic engineering has both risks and the potential to provide significant benefits. The Coordinated Framework for regulation of biotechnology relies on existing federal laws and agencies to assure that genetically engineered products are safe. The goal is to balance the need for safety with the need to avoid impending the

biotech industry. This article reviews U.S. laws of greatest significance to agricultural and food-related biotechnology, and the regulatory roles of FDA, EPA, and USDA's Animal and Plant Health Service. It concludes that consumers, farmers, and the environment are well protected by that system. However, because of the rapid development of biotechnology the regulatory system should be improved, and its underlying strengths better communicated to the public.

Regulation of Genetically Modified Organisms in the European Union, Margaret Rosso Grossman and A. Bryan Endres, University of Illinois at Urbana-Champaign.

To be successful, laws that regulate genetically modified organisms (GMOs) must help society decide rationally when to pause and when to proceed in adopting new biotechnological developments. In the context of European Union (EU) institutions and lawmaking procedures, this article examines European Community (EC) legal measures that govern the contained use, deliberate release and labeling of GMOs. To illustrate Member State implementation of EC measures, the article focuses more briefly on regulation of GMOs in England. It highlights the controversy about GMOs in Member States and reveals some of the deficiencies between U.S. and EU attitudes toward GMOs and genetically modified products.

Environmental Costs and Benefits of Genetically Modified Crops: Implications for Regulatory Strategies, Amy W. Ando and Madhu Khanna, University of Illinois at Urbana-Champaign.

This article sets forth a framework for evaluating the environmental costs and benefits associated with agricultural genetically modified organisms (GMOs), including impacts on plants, humans, animals, and the environment at large. The authors build on this knowledge to explore how and why GMOs should be regulated, highlighting the need for policy makers to bear in mind that genetically modified seeds might substitute for traditional agricultural practices which themselves have detrimental impacts on the environment. To guide regulation formation, the authors present a review of the literature in environmental economics on optimal and second-best regulation, where the latter is used in the face

of real-world complication. They then evaluate how current regulations measure up to those theoretical ideals. Finally, the authors provide some insight into what GMO crop regulation might accomplish by reviewing the evidence on the effects of pesticide regulations.

Intellectual Property Protection and Agricultural Biotechnology: A Multidisciplinary Perspective, Jay P. Kesan, University of Illinois at Urbana-Champaign

Intellectual property (IP) protection makes it possible to exclude others from appropriating the fruits of research and development. At the intersection of biotechnology and intellectual property are several public policy issues concerning innovation, technology, and society (such as social welfare, human health, ecology, and tradition), which must be considered from a multidisciplinary perspective. This article discusses the structure of the ag-biotechnology industry, the role of IP in achieving coordination and sharing of both the benefits and risks of innovation, IP regimes in the U.S. and abroad, and the economic and philosophical rationale for IP. The key principles and doctrines are then applied to specific IP controversies in biotechnology.

Emerging Competition Policy Issues in Agricultural Biotechnology, Michael R. Ward, University of Illinois at Urbana-Champaign.

The increased importance of privately sponsored biotechnology research has led to mergers, strategic alliances, vertical coordination, technology licensing, and other changes among firms within the agricultural sector. The industry is in the midst of sweeping changes, and research and development has become a central driver. Competition concerns are emerging that had not existed in the past and will likely bring increased antitrust scrutiny. This article outlines the economic principles that underlie efficient competition, especially those in high-technology industries. It then uses these principles to analyze the new strategic practices that may trigger increased intervention under competition policy. In particular, the article considers the effects of mergers, research joint ventures, technology licensing, and product tying and bundling.

TECHNOLOGY TRANSFER OF PLANT BIOTECHNOLOGY

Genetically Modified Organisms in Agriculture: Economics and Politics, Gerald C. Nelson University of Illinois at Urbana, USA, ISBN 0125154224, Hardback, 300 Pages, Academic Press, Published March 2001.

Offers a comprehensive overview of the science, economics, and politics of the use of agricultural GMOs. This highly readable book offers in-depth coverage of the three most-widely used GMOs: *Bt* corn and cotton and glyphosate-resistant soybeans. A diversity of views on the GMO controversies are represented, presenting widely different perspectives from leading figures in the debate, e.g., representatives from the EU Commission, Center for Global Food Issues, Consumers' Union, and the Biotechnology Industry Organization.

Features: Additional detailed footnotes and references for the academic community.

International contributions from the U.S., Europe, and India. Covers the perspectives of different groups involved in the controversies: governments, environmental agencies, consumers, industrial agencies, and the developing world.

Genetically Modified Food: Understanding the Societal Dilemma, Edited by Andrew M. Isserman, Sage Periodicals Press, Thousand Oaks, CA, *American Behavioral Scientist* Vol. 44: 8, April 2001, 216 pages.
<http://sagepub.com>

These articles were contributed by 25 faculty members from four colleges at University of Illinois for Important Social Science Research on Biotechnology. They introduce the issue posed by genetically modified foods in two ways. A collection of The New York Times headlines provides a succinct "year in review." Insights drawn from the articles in this issue trace the social dilemma from scientific laboratories through farmers' incentives and concerns to social action and public confusion.

Agricultural Biotechnology and Plant Improvement Setting the Stage for Social and Economic Dialogue, Steven G. Pueppke, University of Illinois at Urbana-Champaign.

The ability to accomplish some novel biology underlies the current dialogue on the social and economic impacts of biotechnology. Using crop plant models, this article sets the scientific context for the discussion that follows in this issue. There are three key messages: changing plants to suit human needs is an ancient and ongoing process; biotechnology makes this process faster and more precise; and the emphasis for biotechnology is increasingly moving toward whole genomes and not just genes. Scientists can enrich the discussion on impacts and acceptance, but as the accompanying articles confirm, science alone is insufficient to provide answers to complex societal questions.

The Risks and Benefits of Agricultural Biotechnology: Can Scientific and Public Talk Meet?, Napoleon K. Juanillo, Jr., University of Illinois at Urbana-Champaign.

The article outlines the direction and tenor of two distinct discourses on agricultural biotechnology. Scientific talk about biotechnology must be seen in the historical context of the status given to science in arriving at knowledge. On the other hand, public talk about biotechnology is largely informed by a number of factors beyond the realm of science and reflects contemporary trends toward the need for public inputs in risk assessment and risk management. Heeding public concerns about risks of agricultural biotechnology may improve communication between scientists and the lay public and consequently lead to better regulatory policies. This article suggests participatory communication as a guide for action. Yet, it recognizes the limits of public participation when public opinion and perception overwhelm the voice of science and become the principal basis for regulatory and policy decisions on agricultural biotechnology.

Some Moral, Ethical, and Transethical Issues Raised by Biotechnology and How We Might Deliberate About Them, Kieran P. Donaghy, University of Illinois at Urbana-Champaign.

The introduction of biotechnology products has been a source of much controversy in large part because of the moral and ethical issues that development and distribution of these products raises. In view of the burgeoning volumes of activity in biotechnology research and development and the far-reaching consequences that biotechnology products may have, there is some urgency to have full and open discussion of these issues. This article identifies a number of the issues that biotechnology has raised and theoretical resources available for aiding deliberation about them. It also sketches a framework for practical reasoning that encompasses many of the issues, and examines the relationship between moral and ethical issues concerning biotechnology and other questions that span or extend beyond ethics.

Roundup Ready Soybean Technology and Farm Production Costs: Measuring the Incentive to Adopt Genetically Modified Seeds, David S. Bullock and Elisavet I. Nitsi, University of Illinois at Urbana-Champaign.

Roundup ready soybean technology (RR) lowers adopters' costs by a) allowing post-emergence use of the inexpensive herbicide glyphosate, b) saving on management costs because of simple use, and c) cutting risk by widening the time window for post emergence spraying. RR lowers non-adopters' costs by creating competition that lowers other herbicides' prices. Our empirical results suggest that for most farms a) is insufficient to cover the RR seed price premium b) and c) must be substantial for many adopters. Preliminary results indicate that RR provides bigger cost savings in the western Corn Belt than in the eastern Corn Belt. Oligopolistic RR suppliers have its price premium higher than potential cost/risk savings on many farms. We conclude that RR will not be fully adopted soon.

Innovation, Supply Chain Control, and the Welfare of Farmers: The Economics of Genetically Modified Seeds, Peter D. Goldsmith, University of Illinois at Urbana-Champaign.

Genetically modified seeds offer farmers dramatic new innovations that revolutionize how they grow crops. An ever more concentrated supply industry is marketing these innovations in novel ways, using technology fees, product bundling, patent protecting contracts, and strict enforcement. Farmers face a choice between dramatic new technologies accompanied by restrictive contracts and conventional technologies readily purchased in a spot market. This article explains why there is greater concentration among seed suppliers, why new marketing arrangements are emerging, and how these conditions might make farmers better or worse off.

Farming Within a Knowledge Creating System: Biotechnology and Tomorrow's Agriculture, Steven T. Sonka, University of Illinois at Urbana-Champaign.

U.S. agriculture is experiencing a time of turbulence. Relatively rapid and substantial changes appear likely, but the timing, nature, and extent of those changes are uncertain. Biotechnology is one, but only one, of several powerful forces shaping the structure of agriculture. This article examines concepts from strategic management and information economics that have proven useful in understanding structural change in other industries. Those concepts are used to improve our understanding of the potential relationships between biotechnology and the structure of agriculture. Doing so emphasizes that, even though forces such as biotechnology appear beyond the reach and control of individuals, their eventual structural effects will be greatly influenced by the actions of farmers, agribusiness managers, and policy makers. The analysis highlights the critically important role of information and management innovations as complementary assets, which will markedly affect biotechnology's eventual impacts on decision making and returns from innovation in the sector.

Social Construction of the Market(s) for Genetically Modified and Nonmodified Crops, Karen L. Bender and Randall E. Westgren, University of Illinois at Urbana-Champaign.

Social processes drive the current market turbulence and the eventual future for biotechnology products in agriculture. We examine those processes using central ideas from the sociology of markets: markets are socially constructed by buyers and sellers, and markets are embedded in the broader sociopolitical environment in which they exist. Those seeking to construct a market for genetically modified soybeans using the existing commodity market as a platform conflict with the sociopolitical environment that withholds normative and regulatory legitimacy from this outcome. The authors conduct a content analysis on recent public dialogue about the problems and pollution in constructing the market(s) for genetically modified soybeans and they apply a model traditionally used in the social construction literature for export analyses of technology adoption. The model proves valuable for identifying pathways for resolving the conflict.

Risk Perception, Behavior, and Consumer Response to Genetically Modified Organisms: Toward Understanding American and European Public Reaction, Carl H. Nelson.

Public debate about the acceptability of genetically modified organisms in the production of food and feed has included controversy about risks of harming human health and/or the natural environment. Consumer and public response to the risks can be volatile, as manifested in some of the extreme protest actions in Europe. These reactions are due, in part, to strong judgments formed from memorable events. Such judgments are common when individuals do not have a good understanding of risks. Economic and psychological theories of decision making provide understanding of how these judgments are formed, how they might evolve, and what can be done to influence them. Public dialogue and action must account for cognitive difficulties assessing risks to stimulate public evaluation that gives full consideration to the benefits and cost of genetically modified organisms.

Social Movement Organizations' Reactions to Genetic Engineering in Agriculture, Ann Elizabeth Reisner, University of Illinois at Urbana-Champaign.

Numerous social movement organizations are actively opposing genetic engineering in agriculture. This article looks at a coalition of movement groups opposing biotechnology and the leading U.S. advocacy groups to determine the breadth of movement resistance. Movements resisting genetic engineering are acting consistently with their previous positions on issues, indicating a high degree of narrative fidelity between belief and action. Furthermore, genetic engineering in agriculture touches on the core concerns of many different types of movements: protecting human health, protecting the environment, and the dangers of monopoly capital controlling a public good such as food. Finally, movement organizations are actively including the core concerns of other types of movements, suggesting the possibility of increased cooperation among different movements.

The Marketing Battle Over Genetically Modified Foods: False Assumptions About Consumer Behavior, Brian Wansink and Junyong Kim, University of Illinois at Urbana-Champaign.

Although proponents assume that good science sells and that biotechnology issue will soon become a non-issue, opponents of biotechnology assume that consumers want to be informed and that the risks of the unknown are more important than benefits. Using current models of consumer behavior, this article examines eight incorrect assumptions about consumers. Understanding the processing style of consumers and how it influences their attitudes suggests changes that both opponents and proponents can make to educate consumers more effectively.

Empowering Stakeholders and Policy Makers With Science-Based Simulation Modeling Tools, James D. Westervelt, University of Illinois at Urbana-Champaign.

Pollen from genetically modified (GM) crops can potentially drift into neighboring non-GM crops. Wind can carry toxin-laden pollen from GM crops into surrounding natural areas. There are warnings that overuse of *Bt* corn (corn in which

genetic material from the bacterium *Bacillus thuringiensis* has been copied) will result in the selection of European corn borer populations that are resistant to *Bt* toxins. Each of these concerns is associated with powerful competing stakeholder interests. The issue will not be solved solely within the scientific community. This article proposes that empowering stakeholders and policy makers with science-based stimulation modeling tools will help bring more science into the policy process than would be possible with scientists only reporting modeling results.

INTERNATIONAL

Agricultural Biotechnology and the Poor-Consultative Group on International Agricultural Research and U.S. National Academy of Sciences, Proceedings of an International Conference, Washington, D.C., 21-22 October 1999, G.J. Persley and M.M. Lantin, Editors, 235 pages.
<http://www.cgiar.org/biotechc/bioconf.htm>

The conference focused on biotechnology and its potential in developing countries, exploring the issues of eradication of poverty and hunger in developing countries that are dependent on agricultural productivity and the descending applications of science and technology to ensure the health of people and environments globally. The conference responded to the pressing need for an open, inclusive, and participatory debate on potential benefits and risks of biotechnology, grounded on scientific evidence and concerned with common good. Key objectives of the conference were to broaden the awareness of developing countries' views on issues related to biotechnology and to contribute to a science-based understanding of the issues and public concerns and how these might be addressed. Ten sections of the conference focused on various aspects.

Current Status of the Agricultural Biotechnology. Biotechnology is a potentially important tool in the struggle to reduce poverty, improve food security, reduce malnutrition, and improve the livelihoods of the rural and urban poor. The exchange of knowledge, information, and experience and the discussion of a variety of sometimes different perspectives will be valuable

in moving ahead with the responsible dialogue and debate on the use of the new developments in science and technology for the benefits of society.

The Role of Science in the 21st Century. Biotechnology has so far been very much a preserve of the richer countries, a fact that distorted the debate on what biotechnology can do for the poor. Moreover, developments in biological science today compel us to confront profound ethical and safety issues, complicated by the new issues of proprietary science.

Feeding the Developing World in the Next Millennium. Biotechnology is one tool in our arsenal for feeding the world in the future. It is a solution not without problems, but we cannot ignore it. We have fallen behind in educating consumers about the potential of biotechnology and in reassuring them about safety concerns. We need to fully assess the risks and benefits of all "new" foods, and when the benefits far outweigh the risk, we need to move ahead. Incentives are needed for research attention to developing country's food crops. Obviously, public good research supported from public funds must be increased.

Analyzing Opportunities and Constraints in Selected Countries. Reports on the current state of biotechnology represented several countries: China, India, Philippines, Thailand, Brazil, Costa Rica, Mexico, Egypt, Iran, Jordan, Kenya, South Africa, and Zimbabwe.

Controlling Environmental Risks. There is public concern worldwide that GE plants might present new risks to the environment. Presented papers outline approaches to a scientific-based risk assessment for plants intended for use in agricultural and other managed environments. The new science of genomics offer a whole new range of options for how land could be used, because crops can be designed to suit the land and the purpose rather than the land being adapted to suit the crop. New sustainable agricultural systems will need to support packages of possible incentives, subsidies, and regulatory measures to make them profitable and attractive to growers. Also, new institutions and multidisciplinary teams are needed to search for more sustainable farming systems, to design

new agricultural systems such as mixing different crops in the same fields, or having nitrogen fixing perennial crops in sustainable perm-cultures. We need to break free from the paradigms of the past where advances in agricultural yield have always meant retreat in sustainability. Problems inherent in developing pest-resistant cultivars that can be sustained, and decrease yield variation were touched on in this report. It will be difficult to spread pest resistant cultivars around the world in a way that increases long-term food security and thereby decreases environmental risks. It must be decided if sustainable pest-protected crops will be a priority in international agricultural search.

Minimizing Health Risks. The assessment of the allergenicity of proteins from unknown allergen sources continues to be a challenge to the food industry. Future efforts must be directed at refining the current technology available. It is possible to identify risks for allergenicity and minimize their effect on exposed populations. The risk/benefit ratio of these new technologies must be considered. The benefits derived from GM crops must be considered against these risks which may vary from country to country. In countries with emerging economies where potential allergies are a lower priority than nutrition, the increased productivity benefits of GM crops may far outweigh any potential risk of allergic reactions.

Minimizing Social Risks. It is crucial that biotechnology be viewed as one part of the poverty alleviation strategy, not as a technological quick-fix for world hunger. Biotechnology needs to go hand in hand with investment in broad-based agricultural growth. Public-sector research is essential for ensuring that molecular biology-based science serves the needs of poor people. It is also urgent that internationally accepted standards and local regulatory capacity be strengthened within developing countries. Evaluation of GM crops needs to increase in developing countries; at present, about 90% of field testing occurs in industrial countries.

Ethics and Biotechnology. The discussion about the contribution of green biotechnology to food security would gain in quality and power of conviction if all who participated were more

balanced in their interventions. An improvement in today's poverty situation in developing countries requires not only good governance, but also more solidarity from the industrial countries with poor people in poor nations. One of the most effective ways of furthering agricultural and hence rural development research will continue to be bringing the cutting-edge research to resource-poor farmers.

Private and Public Sector of Biotechnology Research. Regulatory processes have become clearer in many countries and the private and the public sectors have shown commitments to training and other support. Most importantly, the movement of agricultural technologies beyond the purview of the private-sector originators has often been driven and encouraged by responsible partners who recognized the need for these technologies for the people and areas that they were committed to serving.

Protecting Intellectual Property Rights. Enforceable and strong IPRs are essential to encourage the transfer of the latest technologies to developing countries. They are vital for the modernization of crop production in developing countries. All developing countries should strengthen these rights as soon as possible. For the World Bank and other international development agencies, it is urgent to assist them in this endeavor.

Communicating About Biotechnology and Addressing Public Concerns. As complicated as the subject is, the final public decision about the risks or benefits of biotechnology has been exacerbated in part because in the U.S., at least, people are not used to thinking about questions of agriculture and farming concerns. National discussion has been undermined by food safety scandals and mistrust of the government. The idea that money and business concerns have percolated deeply into biotechnology science suggests that there is reason to think twice before believing public information about biotechnology. Education is important whether it is for reporters or the general public.

Transgenic Plants and World Agriculture, Prepared by members of the Brazilian Academy of Sciences, Chinese Academy of Sciences, Indian National Academy of Sciences, Mexican Academy of Sciences, Royal Society of London, Third World Academy of Sciences and the U.S. National Academy of Sciences, National Academy of Sciences, Washington, D.C., July 2000, 40 pages.
<http://www.nap.ed/html/transgenic>

Report was prepared under the auspices of the Royal Society of London, the U.S. National Academy of Sciences, the Brazilian Academy of Sciences, the Chinese Academy of Sciences, the Indian National Science Academy, the Mexican Academy of Sciences, and the Third World Academy of Sciences (July 2000). Representatives of seven of the world's academies of science have come together to provide recommendations to the developers and overseers of GM technology and to offer scientific perspectives to the ongoing public debate on the potential role of GM technology in world agriculture.

The Need for GM Technology in Agriculture. The conclusion is that steps must be taken to meet the urgent need for sustainable practices in world agriculture if the demands of an expanding world population are to be met without destroying the environment or natural resource base. In particular, GM technology, coupled with important developments in other areas, should be used to increase the production of main food staples, improve the efficiency of production, reduce the environmental impact of agriculture, and provide access to food for small-scale farmers.

Examples of the GM Technology that would Benefit World Agriculture. The authors recommend that transgenic crop research and development should focus on plants that will (i) improve production stability; (ii) give nutritional benefits to the consumer; (iii) reduce the environmental impacts of intensive and extensive agriculture; and (iv) increase the availability of pharmaceuticals and vaccines; while (v) developing protocols and regulations that ensure that transgenic crops designed for purposes other than food, such as pharmaceuticals, industrial

chemicals, etc. do not spread or mix with either transgenic or non-transgenic food crops.

Transgenic Plants and Human Health and Safety. It is recommended by authors that: (i) public health regulatory systems need to be put in place in every country to identify and monitor any potential adverse human health effects of transgenic plants, as for any other new variety. Such systems must remain fully adaptable to rapid advances in scientific knowledge. The possibility of long-term adverse effects should be kept in view when establishing such systems. This will require coordinated efforts between nations the sharing of experience and the standardization of some types of risk assessments specifically related to human health; (ii) information should be made available to the public concerning how their food supply is regulated and its safety ensured.

Transgenic Plants and the Environment. It is recommended by authors that: (i) coordinated efforts be undertaken to investigate the potential environmental effects, both positive and negative, of transgenic plant technologies in their specific applications; (ii) all environmental effects should be assessed against the background of effects from conventional agricultural practices currently in use in places for which the transgenic crop has been developed or grown; and (iii) *in situ* and *ex situ* conservation of genetic resources for agriculture should be promoted that will guarantee the widespread availability of both conventional and transgenic varieties as germplasm for future plant breeding.

Funds for Research on Transgenic Crops-The Balance between Public and Private Sector. It is recommended by authors that: (i) governments should fully recognize that there will always be public interest/goods research requiring public investment even in the market-driven economy; it is imperative that public funding of research in this area is maintained at least at its present level in both CGIAR and national research institutions; (ii) governments, international organizations, and aid agencies should acknowledge that plant genomics research is a legitimate and important object for public funding, and that the results of such research should be placed in the public domain; (iii) innovative and vigorous forms of

public-private collaboration are urgently required if the benefits of GM technologies are to be brought to all the world's people; (iv) incentives are needed to encourage commercial research companies to share with the public sector more of their capacity for innovation; and (v) care should be taken so that research is not inhibited by over-protective intellectual property regimes.

Capacity Building. It is recommended by authors that: (i) national governments ensure that endogenous capacities are built up to facilitate the implementation of biosafety guidelines or regulations; (ii) the safe development, transfer, and application of biotechnology require that nations develop and/or strengthen policies, facilities, information systems, and training in biotechnology (including risk-assessment, risk-management, and biosafety procedures); (iii) nations involved in the development, use, release or production of transgenic plants should have the means to assess and manage the potential risks and the benefits; and (iv) as considered in the recently agreed UN Cartagena Protocol on Biosafety, an overarching body should maintain and disseminate a public database that includes all newly released varieties and their performance in different environments.

Intellectual Property. It is critical that the potential benefits of GM technology become available to developing countries. To this end, it is recommended by authors that: (i) where appropriate, farmers must be allowed to save seed for future use (re-use seed) if they wish to do so; publicly funded research should investigate the value and limitations of re-using seed, and the results of this research should be made freely available to interested parties; (ii) broad intellectual property claims, or claims on DNA sequences without a true invention being made, should not be granted because they stifle research and development; (iii) possible inconsistencies among international conventions, such as those that pertain to patent rights and the Convention on Biological Diversity, should be identified and clarified; (iv) research institutions should establish partnerships among industrialized and developing countries so that the benefits of GM research, applications and licensing will become much

more widely available; and (v) an international advisory committee should be created to assess the interests of private companies and developing countries in the generation and use of transgenic plants to benefit the poor - not only to help resolve the intellectual property issues involved, but also to identify areas of common interest and opportunity between private-sector and public-sector institutions.

Priority Setting in Agricultural Biotechnology Research: Supporting Public Decisions in Developing Countries with the Analytic Hierarchy Process, D. Horton, L. Dupleich, A. Andersen, R. Mackay, and D. Horton, ISNAR Research Report No. 16, July 2000, 110 pages.

<http://www.cgiar.org/isnar/publications/catalog/selected.htm>

The objective of the report was to assess a priority-setting approach to support agricultural research managers in public institutions, especially those in developing countries, through the difficult process of choosing among biotechnology activities.

The report begins with the rationale for public-sector research, analyzing the major trends and challenges that will shape the agenda of public agricultural research organizations. A literature review of the potential role of biotechnology in agricultural research in developing countries is also included. The main difficulties in priority setting for public research are identified, including the multicriteria nature of the public decision-making process measurement and aggregation problems pertaining to different types or research impacts, and a poor information base that is due in part to the forward-looking nature of biotechnology research.

Issues in Biotechnology Research Evaluation. The chapter identifies the factors critical to the design of priority setting processes for biotechnology research. There are three sections in this chapter. The first section outlines rationale for public-sector research and some of the trends and challenges that may shape NARS in future. In the second section, agricultural biotechnology is described insofar as it concerns research in developing countries. In the final section, three

working hypotheses are defined specifically for evaluating research in agricultural biotechnology. The chapter concludes by explaining the requirements that must be met by priority setting procedures: participation, transparency, and a standardized measurement procedure.

Methodological Framework. This chapter explores methodological issues in priority setting. First, the need for formal priority-setting approaches is examined. Then, the different evaluation methods that have been developed for priority setting in agricultural research are reviewed, with a discussion of how they have been implemented in the public research institutions of developing countries. To determine the most appropriate method, the different approaches are analyzed based on the key requirements identified in the previous chapter. Analytic Hierarchy Process (AHP) is then introduced as a methodological tool for priority setting – the first time it has been recommended for decisions support in public agricultural research – and explained in some detail. The final section introduces the methodological framework designed for the priority setting of agricultural biotechnology in public research.

The Chilean Case Study. This chapter describes the pilot application of the AHP-based approach in Chile. The main purpose of the case study was to evaluate AHP as a support tool for decision-making. The evaluation is aimed specifically to testing the ability of the tool of research activities, major uncertainty and the specific characteristics of biotechnology, as discussed in chapter 2. A more general objective is to determine the tool's relevance and viability in terms of taking group decision making and other real-world problems. First, the country selection process is discussed, followed by a brief overview of Chile's agricultural research system. Next, the context of the exercise is provided by a survey of Chile's national biotechnology program, its history and current status. The third section consists of a thorough step-by-step account of the AHP-based procedure, and how it was implemented in the project. Results are discussed in terms of the criteria analysis of the results. This is followed by a critical assessment of the procedure as it was

applied in the case study. The chapter concludes with a few remarks about the positive aspects of the exercise and the shortcomings that need to be addressed for future applications.

Assessment of the Priority Setting Approach. In this chapter, the performance of the AHP-based approach is assessed in terms of its accordance with the working hypotheses, research cost, and other methodological issues. The first three sections examine the value of incorporating the factors that are emphasized by the working hypotheses – the special features of biotechnology, uncertainty, and the strategic component of biotechnology research – into priority setting. The fourth section examines how research costs have been incorporated into the model, and the final section discusses some methodological issues that were raised by this particular application of the AHP –based priority-setting procedure.

Conclusion. Analytic Hierarchy Process was identified as an appropriate methodological tool on which to base the priority-setting approach. It was tested in a pilot application with the national biotechnology program of Chile and positively assessed for usefulness. The three sections of the chapter summarize the major findings of the study. It is structured according to the conceptual, methodological, and procedural issues that were encountered.

World Food Security and Sustainability: The Impact of Biotechnology and Industrial Consolidation, NABC Report 11, National Agricultural Biotechnology Council, Ithaca, New York, December 1999, 180 pages.

http://cals.cornell.edu/extension/nabc/pubs/nabc_11.pdf

An Overview by Donald P. Weeks, University of Nebraska-Lincoln.

The 1999 NABC meeting explored new developments in agricultural biotechnology and trends toward industrial consolidation in agriculture. A goal of the workshops was to develop consensus statements regarding the nature of current trends and the implications of these trends on the structure and sustainability of

agriculture in North America, as well as the rest of the world.

Securing and Sustaining Adequate World Food Production for the Third Millennium.

Per Pinstруп-Andersen, an economist from the World Bank, furnished perspectives on the future in regard to population, food, and agriculture worldwide. Among emerging issues forecast by Pinstруп-Andersen were the following: a potentially strong backlash (especially in developing countries) to the globalization and consolidation of agricultural businesses; an absolute necessity to use modern science and technology to meet the growing food demands of the world; the likelihood that water may become the limiting factor in food production in the near future; concerns that the scare over food safety and health risks (especially in Europe) resulting from bacterial contaminations and mad cow disease may be lumped together with concerns over genetically modified foods — the consequences of which could be exclusion of people in developing countries from increased food supplies that could be made available through agricultural biotechnology.

Using Biotechnology to Enhance and Safeguard the Food Supply:

Delivering the Benefits of the Technology. John Pierce of DuPont provided a view on things to come in agricultural biotechnology in regards to products and in regard to business implications. In his summary, Pierce pointed to several ways that biotechnology is enhancing and safeguarding food suppliers. These include crops with higher yield potential, genetically modified crops that allow for more environmentally friendly farming practices, feeds for livestock and poultry that are more nutritious and more efficient and crops that offer improved economic benefits for producers, processors, and consumers.

Agricultural Biotechnology: Social Implications and Integration of Landscape and Lifescape.

Cornelia Flora of Iowa State University provided an overview of trends in social and economic conditions that are affecting the degree to which the products of agricultural biotechnology are accepted. Flora discussed six trends she saw as affecting the markets for

the products of agricultural biotechnology: globalization, industrialization, decentralization, privatization, polarization, and engagement.

Policy and Technology as Factors in Industry Consolidation.

Stan Johnson of Iowa State University provided an overview of policy and technology factors involved in industrial consolidation. Johnson found industrial consolidation would continue in the foreseeable future with more and more power held and exerted by multinational companies. He also found that funding for public research would decrease, as well as the rate of scientific discovery and technology development in agriculture.

Evolving Business Strategies to Utilize Development in Biotechnology Supporting Long-Term Production of Adequate Supplies of High-Quality Food for the World.

James Tobin of Monsanto provided an industry perspective on agricultural biotechnology, emphasizing challenges that face agriculture and agricultural biotechnology in the coming years: the task of feeding two billion more people in the next 30 years, which is imperative to improving the quality and nutrition provided by crops in the future, and the challenge of farming with more respect for the environment. Agricultural biotechnology was seen by Tobin as facing multiple challenges: consumers' political acceptance in Europe; intense competition; and rapid changes in the technology.

Biotechnology on the Ground: What Kind of Future Can Farmers Expect and What Kind Should They Create?

Fred Kirschmann, organic farmer, stated that the promise of agricultural biotechnology is threefold: increase in profitability, benefit in pest control, and help to feed the world. In regard to the latter point, he posited that hunger is not so much a problem of food supply as it is a problem of food distribution. As for the pest management, "therapeutic intervention" with pesticides is being questioned because such systems are inherently short lived. He encouraged adoption of a restructured approach in which natural pest management systems are employed. With the push toward consolidation of the agriculture industry into perhaps as few as four "food clusters" that will control food production,

processing and distribution, contract farming and control of farmers through contracts will spread widely.

Why Biotechnology May Not Represent the Future in World Agriculture. Dennis Avery of Hudson Institute declared that environmentalists and anti-technology groups were winning almost every confrontation by appealing to urban audiences in developed countries who are well fed and have been taught to appose anything that is not natural, organic, or that uses newly developed, not fully tested, technology. He cautioned that there might be important consequences to their choices – mounting world populations and increase in demand for more food and higher quality food.

Meeting Food Needs through Sustainable Production Systems and Family Farms. A markedly different perspective of the future of rural communities and farming was provided by Chuck Hasserbrook of the Center for Rural Affairs. Hasserbrook contended that family farms and sustainable systems can feed the world into the foreseeable future. How well this goal is achieved depends on how well the society invests in the research that is necessary to allow family farming and sustainable agriculture to succeed. Hasserbrook urged that the focus of public university research is changed to bring it on track with “public good” needs of people. To date, university research has focused largely on development of new products for the supply site of agriculture. No social system will survive that does not consider all the people that have a stake in the system.

Biotechnology and Mature Capitalism. William Hefferman of the University of Missouri predicted that, while agricultural biotechnology may have great promise for improving our means of feeding the hungry people of the world, the system into which its results must be funneled may prevent the promise from being fulfilled. Hefferman pointed to the rapid shift to a system of highly centralized control of food processing industry and distribution. He urged greater investment in sociological research on food distribution systems as a key to solving the vexing problems of today and the future.

Changing Consumer Demands Can Drive Biotechnology Adoption. Susan Offutt of the USDA/Economic Research Service focused on the role of the consumer in driving much of what is happening in agricultural biotechnology and its associated industries. Understanding consumer demand is key to understanding the move from commodity agriculture to product-driven business. Offutt cautioned meeting participants not to demonize or lionize any one actor that may be at play in the free market system, but urged everyone to understand “causality” as the driving force in the marketplace.

The Federal Role of University Sponsored Agricultural Research and Resolving Conflicts Arising Out of the Implementation of New Technologies. Cliff Gabriel of the White House Office of Science and Technology talked about the role of the federal government programs and policies in agricultural biotechnology. He pointed out the role of Land Grant institutions in performing research that has made invaluable contributions to the nations. However, the partnership between universities and the government has been subject to growing stress, which led to a new set of principles for the partnership that recognizes that research is an investment in the future, that linkage between research and education is vital, that peer review is essential to excellence in research, and that research must be conducted with integrity.

Where Do We Go From Here? The View from Times Square. Paul Raeburn of Business Week emphasized that the bulk of urban dwellers were not at all aware that a high percentage of crops in America are now genetically engineered. He suspects that these people won't be happy about being fooled in regard to their food. He suggested that it might be wise that the issue of labeling was faced quickly and effectively.

Workshop A: Promises and Problems Associated with Agricultural Biotechnology. In the first of three successive sessions, the participants initially listed over 50 “promises” offered by biotechnology to agriculture and world food supplies and, likewise, over 40 potential “problems” associated with the use of biotechnology in agriculture. In a second session, they identified

what they considered the promises and problems of greatest significance. In the final session, delegates worked together to assemble consensus statements and potential policy recommendations upon which they could agree.

Workshop B: Potential Promises and Problems Associated with Changing Business Strategies in Agriculture. The participants in the workshop B focused on the following questions: What new trends are seen in business strategies related to agricultural food production and distribution? How is biotechnology contributing to these changes? What are the perceived promises and problems associated with the new business strategies?

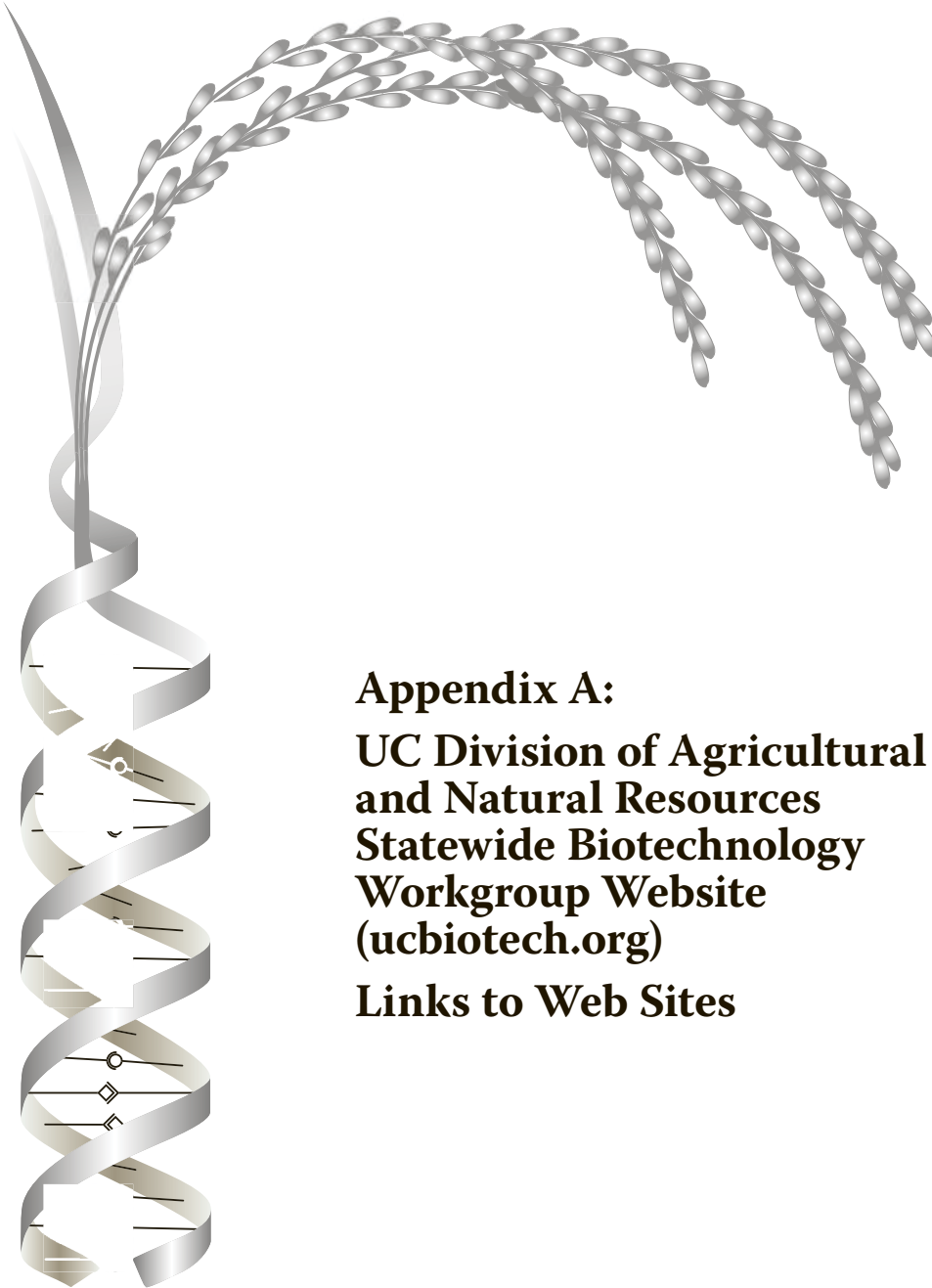
FUTURE USES

Harvest on the Horizon: Future Uses of Agricultural Biotechnology, prepared by the Pew Initiative on Food and Biotechnology, September 2001, 105 pages.
<http://pewagbiotech.org/research/harvest/harvest.pdf>

This report provides an illustrative overview of what could be the “next generation” of genetically engineered agricultural products in two sections; Part I. Plants and Part II. Animals. Much of the research cited is at an early stage and many of the applications face significant technical, economic, marketing, and regulatory issues before they can be brought to market. In this report, the term “biotechnology” refers to the use of recombinant DNA technology to take genes from one organism and insert them into the DNA of another plant or animal. Over the last decade, scientists’ ability to alter the traits of plants and animals by moving genes from one organism into another has come out of the laboratory into the mainstream domestic agriculture. To date, scientists have largely used this technology to create crops that benefit farmers, such as corn and cotton capable of fending off destructive pests, and soybeans resistant to chemical herbicides. Now, however, in numerous universities and company laboratories, the power of biotechnology is being used to modify agricultural plants and animals for a wider array of purposes. The ability to cross the species boundary is not entirely new. In the wild, tree species such as poplar and oak have been known to naturally create hybrids. Scientists using conventional hybrid breeding

techniques have also been able to cross species of wheat and rye. Modern biotechnology, through its ability to directly transfer selected genetic material, greatly increases the potential to move genes between species and creates new possibilities to move genes across very distant species, phylas, or kingdoms. The major focus of current agricultural science is on genomics — the systematic investigation of animal and plant genomes. Mapping genomes makes it easier for scientists to locate comparable genes in different species. The expanding number of genome maps reveals the striking commonality among living organisms. To date, scientists and researchers have sequenced 48 genomes.

The potential benefits to traditional agricultural problems are making it easier to produce food, grow food with improved quality and nutrition, and use agriculture to meet non-food needs such as fiber, fuel, and other products. Research on the modification of animals has produced human proteins aimed at expanding the range of proteins suitable for human medical therapy. To date, scientists have produced human proteins in sheep, pigs and goats. Bioengineered animals may also be useful in creating new vaccines for diseases and the production of tissues and organs in animals for use in humans. Other applications of genetic modification in animals include inducing more rapid growth or weight gain, altering milk to reduce lactose, improving shelf life or increasing disease resistance. Genetically engineering of fish and other aquatic species has focused on enhanced growth, stress resistance, disease resistance, and sterility. Genetic engineering techniques have been applied to insects to develop insect viruses for use as biopesticides and controlling transmission of human and animal diseases. Summary charts are provided for genetically engineered food crop products, tree products, grass and flower products, industrial products, pharmaceuticals and environmental remediation, mammals, aquatic organisms, and insects. The charts list objective, solution and status of research along with some excellent illustrations of techniques and a glossary of terms. This report is not an endorsement for future applications, but is intended to help inform the debate by illustrating the range of potential uses of agricultural biotechnology being explored by scientists.



**Appendix A:
UC Division of Agricultural
and Natural Resources
Statewide Biotechnology
Workgroup Website
(ucbiotech.org)
Links to Web Sites**

Appendix A: UC Division of Agricultural and Natural Resources Statewide Biotechnology Workgroup Website (ucbiotech.org)

LINKS TO WEBSITES

Providing links to outside sites is not an endorsement of their contents	<i>Bt</i> backgrounder http://www.plant.uoguelph.ca/safefood/gmo/updated-Bt-backgrounder.htm
GENERAL BIOTECHNOLOGY INFORMATION	Bioethics, Prof. Gary L. Comstock http://www.public.iastate.edu/~comstock/homepage.html
The International Food Information Council Foundation, Washington, D.C. http://ifcinfo.health.org	Ecological Impact Assessment, CAST (Council for Agricultural Science and Technology) http://www.cast-science.org/biotechnology/20001011.htm
Historical Timeline of Biotechnology http://www.ncbiotech.org/aboutbt/timeline.cfm	Iowa Grain Quality Initiative http://www.extension.iastate.edu/Pages/grain/gmo/gmocklist.html
Information Systems for Biotechnology http://www.nbiap.vt.edu/	Soybean.com http://www.soybean.com/bseries.htm
AgBiotechNet http://www.agbiotechnet.com/	Transgenic Crops, Colorado State University http://www.colostate.edu/programs/lifesciences/TransgenicCrops
Agnews of the Texas A&M University Agriculture Program http://agnews.tamu.edu/	National Biotechnology Information Facility http://www.nbif.org
US National Agricultural Library http://www.nal.usda.gov/bic	The WWW Virtual Library, biotechnology information directory http://www.cato.com/biotech/
CropGen http://www.cropgen.org/databases/cropgen.nsf	AbBioWorld.org http://www.agbioworld.org/
Agrichemical and Environmental news http://www.tricity.wsu.edu/aenews/	Elsevier Science powerful Internet search tool Scirus http://www.scirus.com/
Scientific and industrial research for Australia (search for Biotechnology) http://www.csiro.au/	
AfricaBio http://www.up.ac.za/academic/fabi/africabio/	

SELECTED INTERNATIONAL ORGANIZATIONS

CGIAR

<http://www.cgiar.org/>

FAO

<http://www.fao.org/>

ISAAA

<http://www.isaaa.org/>

The World Bank

<http://www.worldbank.org/>

Rockefeller Foundation

<http://www.rockfound.org/>

Dietary Supplement Information Bureau

<http://www.supplementinfo.org>

Biotechnology Information Centre, Malaysia

<http://www.bic.org.my>

GENERAL AGRICULTURE AND FARMING

InterNutrition (German)

<http://www.internutrition.ch/in-news/mediainfo/index.html>

Health-relevant and environmental aspects of different farming systems: "organic, conventional and genetic engineering"

SELECTED RESEARCH SITES

Biotechnology at Iowa State University (USA)

<http://www.biotech.iastate.edu/>

Biotechnology at University of California, Davis (USA)

<http://www.biotech.ucdavis.edu/home/BioTechatUCD.asp>

Boyce Thompson Institute for Plant Research (USA)

<http://bti.cornell.edu/>

Crop Biotechnology Center, Texas A&M University (USA)

<http://cbc.tamu.edu/>

Department of Plant and Microbial Biology, University of California, Berkeley (USA)

<http://plantbio.berkeley.edu/>

Department of Plant Biology, Ohio State University (USA)

<http://www.biosci.ohio-state.edu/~plantbio/plantbio.html>

Donald Danforth Plant Science Center, St. Louis (USA)

<http://www.danforthcenter.org/index.html>

European Molecular Biology Laboratory

<http://www.embl-heidelberg.de/>

Institute for Plant Sciences, ETH Zurich (Switzerland)

http://www.rereth.ethz.ch/agrl/pflanzen/pflanzen.prof_overview.html

John Innes Centre, Norwich (UK)

<http://www.jic.bbsrc.ac.uk/>

Max-Planck-Institut fuer Zuechtungsforschung, Koeln (Germany)

<http://www.mpiz-koeln.mpg.de/>

North Carolina Biotechnology Centre (USA)

<http://www.ncbiotech.org/>

Roslin Institute Online (UK).

<http://www.ri.bbsrc.ac.uk/>

Scottish Crop Research Institute (UK)

<http://www.scri.sari.ac.uk/>

University of Illinois Biotechnology Center (USA)

<http://www.life.uiuc.edu/biotech/index.html>

University of Missouri (USA)
<http://cafnr.missouri.edu/>

Wageningen Agricultural University,
Wageningen (Netherlands)
<http://www.wau.nl/welcome.html>

SELECTED SOCIETIES AND ORGANIZATIONS

EFB Task Group on Public Perceptions of
Biotechnology
<http://efbweb.org/ppb>

European Plant Biotechnology Network
<http://www.epbn.org/>

EUFIC
<http://www.eufic.org/>

EUROPA-BIO (European biotech industry
organization)
<http://www.europa-bio.be>

Food Biotechnology Communications Network
<http://www.foodbiotech.org/>

International Association for Plant Tissue
Culture & Biotechnology
<http://www.hos.ufl.edu/iaptcb/>

International Food Information Council
<http://ifinfo.health.org/>

International Society for Molecular Plant-
Microbe Interactions
<http://www.scisoc.org/ismpmi/>

International Society for Plant Molecular Biology
<http://www.uga.edu/~ispmib/>

National Agricultural Biotechnology Council
<http://www.cals.cornell.edu/extension/nabc/>

National Corn Growers' Association (USA)
<http://www.ncga.com/>

Biotechnology Links in California
Bay Area Biotechnology Education Consortium
<http://www.babec.org/default.htm>

Biotechnology Program UC Davis
[http://www.biotech.ucdavis.edu/home/
BioTechatUCD.asp](http://www.biotech.ucdavis.edu/home/BioTechatUCD.asp)

California Institute of Food and Agricultural
Research
<http://www.cifar.ucdavis.edu>

California Science Teachers Association
<http://www.cascience.org/Default.htm>

Agriculture and Natural Resources (DANR),
University of California
<http://danr.ucop.edu/>

Food Safe Program
<http://foodsafe.ucdavis.edu/>

Center for Consumer Research
<http://ccr.ucdavis.edu/>

UC Systemwide Biotechnology Research and
Education Program
<http://www-biotech.berkeley.edu/>

Seed Biotechnology Center at UC Davis
<http://sbc.ucdavis.edu>

Website of the Center for Sustainable Resource
Development at UCB
<http://www.CNR.Berkeley.EDU/csrd/>

CEPRAP
<http://ceprap.ucdavis.edu/cephome.htm>

SELECTED EDUCATION SITES

DNA Learning Center, Cold Spring Harbour
Laboratories
<http://vector.cshl.org/>

European Initiative for Biotechnology Education
<http://www.rdg.ac.uk/EIBE/>

Educational Resources Iowa State University
<http://www.biotech.iastate.edu/Educationalresources.html>

National Center for Biotechnology Education
(UK), practical biotechnology protocols
<http://www.ncbe.reading.ac.uk/NCBE/PROTOCOLS/PRACBK/menu.html>

CEPRAP Biotechnology Kit, University of
California, Davis
<http://www.aes.ucdavis.edu/outreach/univout/programs/biokit.htm>

AccessExcellence
<http://www.accessexcellence.org/>

SCOPE: Science Controversies on-line
<http://scope.educ.washington.edu/>

Biotechnology Institute
<http://www.biotechinstitute.org/order.html>

Biotechnology Outreach Program of the
University of Wisconsin
<http://www.biotech.wisc.edu/Education/>

Ag in the Classroom
<http://www.agclassroom.org/teachres/links/biotech.htm>

Education World
<http://www.education-world.com/>

Biotechnology Project of the University of
Nebraska
<http://ardc.unl.edu/aboutbiotech.htm>

<http://biotech-adventure.okstate.edu/>

An educational website designed to present the factual information regarding biotechnology in a way that will entertain and hold the interest of students and adults. Educational illustrations, short videos and animations are provided in a format that can be downloaded by teachers and other educators for use in their curriculum. Fun and informative!

GOVERNMENT SITES

National Institutes of Health, Office of Dietary
Supplements
<http://ods.od.nih.gov/publications/publications.html>
<http://ods.od.nih.gov/news/news.html>

Agriculture & Agri-Food Canada
<http://www.agr.ca/cb/biotech/biotece>

Biotechnology Information System (BTIS)
Department of Biotechnology (DBT), India
<http://dbtindia.nic.in/btis/>

European Patent Office
<http://www.epo.co.at/index.htm>

EU Biotechnology Program
<http://europa.eu.int/comm/research/biot1.html>

National Center for Biotechnology Information
(USA)
<http://www.ncbi.nlm.nih.gov/>

US Department of Agriculture
<http://www.aphis.usda.gov/biotech>

US Environmental Protection Agency
<http://www.epa.gov>

US Food and Drug Administration
<http://www.fda.gov>

US Patents and Trademark Office
<http://patents.uspto.gov/>

National Agricultural Library
<http://www.nal.usda.gov/bic/>

COMPANIES INVOLVED IN BIOTECHNOLOGY

Aventis
<http://www.aventis.com/>

BASF
<http://www.basf.de/>

Bayer Corporation
<http://uscrop.bayer.com/>

DeKalb Genetics Corporation
<http://www.dekalb.com>

Deltapine Seed
<http://www.deltapinseed.com/>

EDEN Bioscience Corporation
<http://www.edenbio.com>

Genetic ID
<http://www.genetic-id.com>

Monsanto Agricultural Company
<http://www.monsanto.com>

Northrup King Co.
<http://www.nkseeds.com/>

Novartis International AG
<http://www.novartis.com>

Pioneer Hi-Bred International
<http://www.pioneer.com>

Syngenta
<http://www.syngenta.com/>

BROADER PERSPECTIVE

BIO
<http://www.bio.com>

Consumers International
<http://www.consumersinternational.org>

Council for Biotechnology Information
<http://www.whybiotech.com/main.html>

DuPont's Straight Talk About Biotechnology
<http://www.dupont.com/biotech>

English Nature
<http://www.english-nature.org.uk/>

Friends of the Earth
<http://www.foei.org/>

Greenpeace
<http://www.greenpeace.org/~geneng/index.html>

Institute of Science in Society
<http://www.i-sis.org/>

Junkscience.com
<http://www.junkscience.com/>

Natural Law Party genetic engineering pages
<http://natural-law.ca/genetic/geindex.html>

National Organic Program
<http://www.ams.usda.gov/nop/>

Pure Food campaign
<http://www.purefood.org>

Rural Advancement Foundation International
<http://www.rafi.org/>

Union of Concerned Scientists
<http://www.ucsusa.org>

Physicians and Scientists for Responsible
Application of Science and Technology
<http://psrast.org>

BIOTECHNOLOGY LINKS IN SWITZERLAND

BAG Bundesamt für Gesundheit
<http://www.admin.ch/bag>

BATS Biosicherheitsforschung und
Abschätzung von Technologiefolgen des
Schwerpunktprogrammes Biotechnologie
<http://www.bats.ch/>

B.I.C.S. Informationstelle des
Schwerpunktprogrammes Biotechnologie
<http://www.bics.ch/>

BUWAL Bundesamt für Umwelt, Wald und
Landwirtschaft
<http://www.buwal.ch>

ETH Zuerich, Institut fuer
Pflanzenwissenschaften
<http://www.ipw.agrl.ethz.ch/>

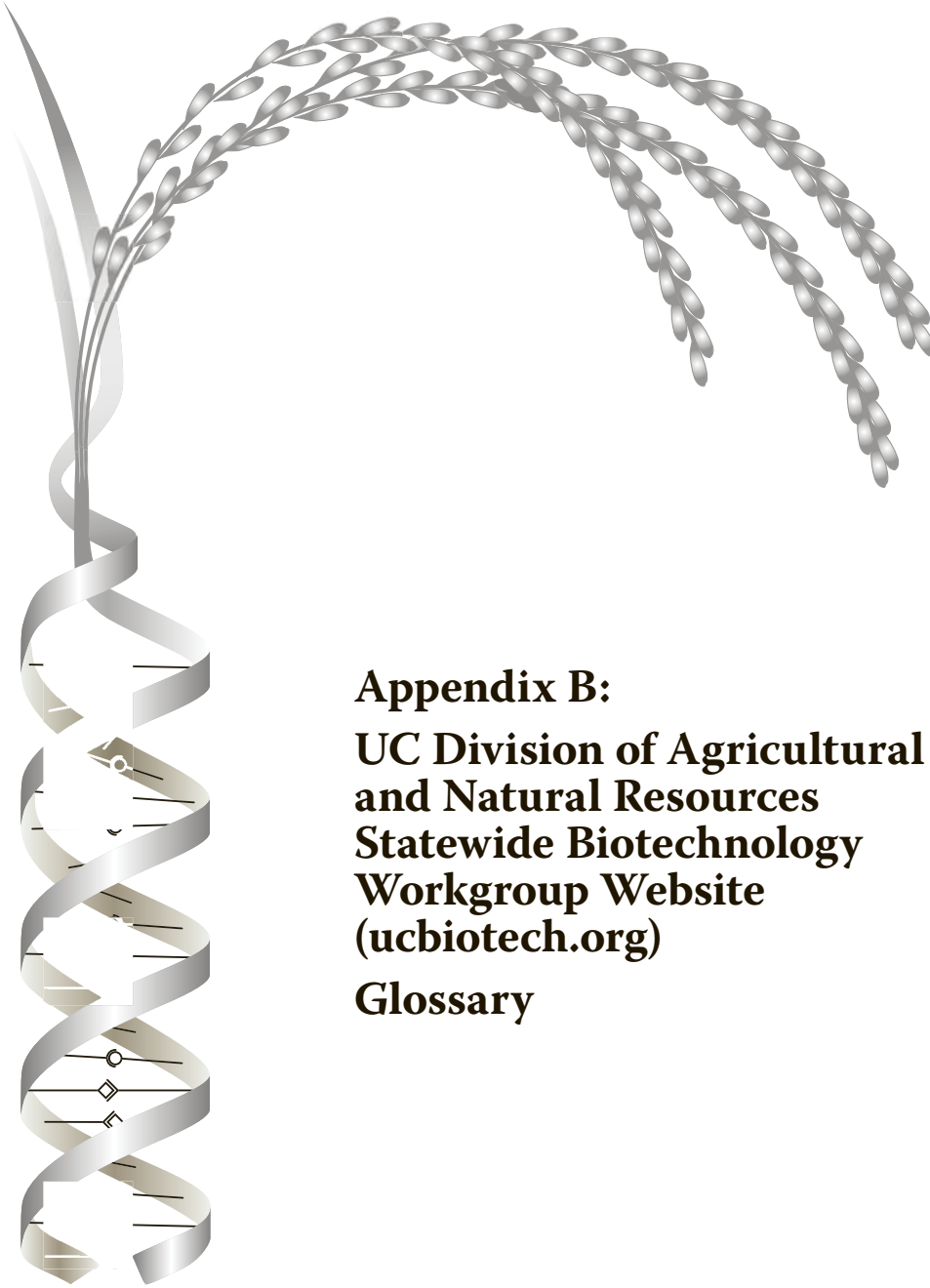
Gen Suisse
<http://www.gensuisse.ch/>

Internutrition
<http://www.internutrition.ch/>

Interpharma
<http://www.interpharma.ch/>

Junge Forschende für eine verantwortungsvolle
Gentechnologie (JFvG)
<http://www.jfvg.unizh.ch>

Modified Tuesday, December 11, 2001



**Appendix B:
UC Division of Agricultural
and Natural Resources
Statewide Biotechnology
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(ucbiotech.org)
Glossary**

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Agrobacterium

Microorganism (bacterium) that produces crown gall disease in the wild; it does so by introducing a part of its genetic material into the plant to direct it to make compounds it needs to live. A small piece of genetic material was isolated from this bacterium.

Agro-ecosystem

A complex mixture of pastures, farm fields, businesses, home sites, natural habitats, and cities and towns.

Agronomy

The science and economics of crop production; management of farm land.

Antibiotic

Chemical sometimes synthesized by other organisms, sometimes manufactured, that is a deterrent to other organisms.

Antibiotic resistance

Resistance mechanisms to antibiotics exist that render cells “immune” to the antibiotic; the genes for these characteristics are found in certain organisms. The genes are used in some genetic engineering experiments as tools to identify cells that have received new DNA.

Antibody

Protein produced by humans and higher animals in response to the presence of another protein, termed an antigen. The interaction of the antigen and the antibody can cause certain human health problems, like allergies or autoimmune diseases.

Antigen

Substance, usually a protein, that when introduced into the body causes the body to make an antibody, usually specific to the antigen.

Autoradiography

Technique used to visualize DNA that is labeled with radioactivity. It can be used to determine the presence or absence of certain DNA fragments and the length or number of DNA molecules.

Bacillus thuringiensis

See *Bt*

Bacteriophage

Virus that infects bacteria, sometimes causing the death of the host organism.

Bacterium/pl. bacteria

Simplest form of life that exists as a single cell without a distinct structure called a nucleus that contains the genetic information of the cell. Also known as a prokaryote.

Base pair

One unit of DNA composed of two complementary nucleic acid molecules (nucleotides) on opposing strands of DNA. The base adenosine always pairs with thymidine; the base guanine pairs with cytosine.

Biodegradable

Capable of being broken down by microorganisms. Breakdown products can often be re-used by other organisms as food and energy sources.

Bioinformatics

Assembly of data from genomic analysis into accessible and usable forms.

Biomass

Total weight of all organisms in a sample after drying.

Biomining

Use of living organisms (e.g., bacteria, plants) to accumulate in their cells precious metals, like gold, silver, platinum, from mine tailings. Organisms can be collected and the metal recovered.

Bioreactor

Vessel or container in which a biological reaction occurs. Often used in manufacturing efforts to produce pharmaceuticals.

Bioremediation

Use of organisms (e.g., bacteria, plants) to remove environmental contaminants from soils and water. The contaminants can include organic molecules, like PCB's, or metals, like mercury, selenium and lead.

Biotechnology

Historically means use of an organism to perform a function, like making cheese or wine. Contemporary meaning includes the use of the new genetic tools of recombinant DNA to make a new genetically modified organism.

BST/BGH

Bovine somatotropin or bovine growth hormone. This is a hormone produced by cattle naturally. The genetic information for this hormone was cloned and can now be made in microorganisms for injection into cattle to increase milk production.

Bt

Bacillus thuringiensis. A naturally occurring microorganism that produces a toxin that only kills organisms with alkaline stomachs, namely insect larvae. As a whole killed organism, this toxin has been used for biological control for decades. The genetic information that encodes the toxin was identified and moved into plants to make them insect tolerant.

“Bug”

Colloquial or slang term for bacterium.

Callus

Undifferentiated plant cells resulting from cell division of differentiated organs, such as leaves, roots, and seeds. The undifferentiated callus can be triggered by hormones to develop into a whole plant.

cDNA

DNA that is synthesized to be complementary to a mRNA molecule. By definition a cDNA represents a portion of the DNA that specifies a protein (is translated). If the sequence of the cDNA is known, by complementarity, the sequence of the DNA is known.

Cell

Basic unit of life, the smallest living structure that is able to function independently. The human body is composed of trillions of cells; bacteria are a single cell.

Centimorgan

Unit of measurement for studying genetics. One centimorgan is equivalent to a 0.01 chance that a particular genetic location (locus) will be separate from a particular marker in a single generation. In humans a centimorgan is about 1 million base pairs.

Chromosome

Spring-like structures of tightly coiled DNA that contains the genetic information (genes) that instructs the cell on its function. Genes are present on chromosomes. Organisms contain differing but characteristic numbers of chromosomes; humans contain 23.

Clone

Exact genetic replica of a single unit of the genetic information in the form of DNA (e.g., gene) or of an entire cell or organism.

Cloning

Means of isolating particular parts of the genome in small fragments of DNA and making copies of and studying the sequence in another organism. Can also mean the process of producing by nonsexual means an identical copy of an organisms.

Codon

Unit of three nucleotide bases contained in the DNA and mRNA that specifies the information for one of the 20 amino acids; the entire array of codons is known as the genetic code. Strings of codons form genes and strings of genes form chromosomes.

Contigs

Group of DNA sequences that are overlapping or contiguous on the genome. Such sequences are necessary to obtain the entire, uninterrupted sequence of the genome.

Cosmids

Vehicles that are used to separate out discrete sections of the DNA for cloning purposes. These vehicles contain bacterial phage lambda DNA to allow them to make copies of themselves in their bacterial host and also DNA fragments of about 40,000 base pairs from the source being studied.

Cross-infection

The simultaneous infection with different types of viruses.

Culture

A particular type or subset of organisms growing under controlled conditions in the laboratory; a cell culture.

Cytoplasm

Liquid portion inside of a cell in which other parts of the cell reside, e.g., ribosomes, mitochondria.

Dietary supplement

Food product ingested to correct a perceived deficit in the overall diet; typically not a whole food.

DNA

Deoxyribonucleic acid. The chemical building block of the genetic information in the cell, genes; it specifies the characteristics of most living organisms. The DNA is usually in the form of two complementary strands.

DNA probe

Short piece of DNA that is complementary to a specific piece of DNA in the cell. By marking the probe, it is possible to visualize whether the DNA is present in the genetic material. This forms the basis for DNA diagnostics.

E. coli/Escherichia coli

Specific single-celled organism or bacterium that lives in the intestinal tract of most vertebrates; some strains of this bacteria are harmful to humans, e.g., *E. coli* 0157. This organism has been used to do much of the genetic manipulation with recombinant DNA methods because it is well-characterized genetically.

Ecology

Study of interaction of organisms with the physical environment and with one another.

Ecosystem

Living system that includes all organisms in a "natural community" that live and interact with their environment.

Electrophoresis

Method using an electrical field which leads to the separation of proteins or DNA fragments based on their size. Smaller proteins or DNA fragments move faster; larger ones slower. Samples are normally placed in the electrical field loaded in a gel-like substance, called agar or agarose.

Endophyte

Organism living inside another organism. In some cases the endophyte cannot live outside its host, an “obligate endophyte”; in other cases the endophyte can live outside its host, “facultative endophyte”.

Enzyme

Protein that facilitates or speeds up certain chemical reactions. Enzymes are used inside of cells to aid in cell growth and reproduction. Enzymes have also been isolated from organisms and used in products like cheese and laundry detergents.

Eucaryote/eukaryote

Organism that contains a defined nucleus; includes all organisms except viruses, bacteria and blue-green algae, which are known as prokaryotes.

Exons

Portion of the DNA sequence that codes for the protein parts of the gene.

Explant

Portion of living tissue that is removed from the organism (e.g., plant) and cultured independently in the laboratory.

Fermentation

Conversion of one substance into a more desirable substance through the actions of microorganisms under controlled growth conditions.

Functional food

Food that provides health benefits beyond energy and essential nutrients (e.g. yogurt, which promotes beneficial microflora in the gut).

Fungicide

Some agent, like a chemical, that kills fungi.

Fungus/ pl. fungi

Type of microorganism that lacks chlorophyll used for photosynthesis, for example yeasts and molds.

Gene

Segment of DNA specifying a unit of genetic information; an ordered sequence of nucleotide base pairs that produce a certain product that has a specific function.

Gene flow

The incorporation of genes from one organism into the complement of genes in another population of organisms.

Gene mapping

Determination of the relative locations of genetic information (genes) on chromosomes.

Gene pool

The combination of all genes and gene variations of a specified group, e.g. species.

Genetically modified organism (GMO)

Term used to refer to organisms modified by the new methods of genetic engineering.

Genetics

Study of the patterns of inheritance of genetic information in organisms.

Genome

Entire genetic material in an organism, comprising all chromosomes.

Genomic library

Collection of DNA clones that represent the entire genome.

Genomics

Molecular characterization of all the genes and gene products of a species.

Genotype

Collection of genetic material in an organism that gives rise to its characteristics.

Herbal supplement

The subset of botanical supplements derived from herbaceous plants.

Hybridization

1. Joining of two complementary strands of DNA, or of DNA and RNA, to form a double stranded molecule. 2. Process of sexual exchange between two plants to produce hybrid plants.

Intellectual Property

Intellectual Property rights include patent rights, plant variety protection certificates, unpublished patent applications and inventions that may or may not be legally protectable.

Intron

DNA sequences that interrupt the protein-coding sequence of a gene; introns are transcribed into mRNA but the sequences are eliminated from the RNA before it is used to make protein.

Immunoassay

Diagnostic assay that uses antibodies to confirm the presence/absence of certain compounds.

In vitro

Direct translation is "in glass". Describes biological reactions that take place in laboratory containers, such as test tubes. Although they attempt to achieve conditions in living organisms, such reactions only simulate real-life situations.

In vivo

Direct translation is "in life". Describes biological reactions taking place inside living organisms.

Library

Collection of fragments of the genome in an unordered array. Relationships of fragments can be determined by physical (sequencing, RFLP maps, ESTs) or genetic means.

Linkage

Physical relationship between markers on a chromosome; the linkage number gives an estimate of the probability that two markers will be inherited together. The closer together the markers, the lower the probability that they will be separated during chromosome pairing after fertilization.

Locus

Location of a gene on a chromosome.

Marker

Identifiable physical location on a chromosome, the inheritance of which can be monitored.

Marker gene

Gene used during genetic engineering attempts that helps to identify cells that have received new DNA. Genes usually include either a selection advantage, e.g., antibiotic or herbicide resistance, or visualization advantage, e.g., beta glucuronidase (GUS) or green fluorescent protein (GFP) expression.

Metabolites

Substances that are used by or produced by enzyme reactions or other metabolic processes.

Microbe

Any small, microscopic organism.

Micrometer

Unit used for measurement, equivalent to 10^{-6} meters or one-millionth of a meter; abbreviation μm .

Molecular breeding

Identification and evaluation of useful traits in breeding programs using marker assisted selection.

Monoclonal antibody

Highly specific, purified antibody derived from only one subset of cells and which recognizes only one antigen or epitope.

Morphology

Form and structure of organisms, like plants and animals; their structural appearance.

Mutagen

Agent or process that causes mutation, like chemicals, radiation or transposable elements.

Mutant

Variant organism that differs from its parent because of mutation.

Mutation

Genetic change caused by natural phenomena or by use of mutagens. Stable mutations in genes are passed on to offspring; unstable mutations are not. From latin word for “change”.

Mycorrhiza/pl. mycorrhizae

Fungal microorganisms that form close, symbiotic relationships with the roots of higher plants. Such relationship often provide the plant with micronutrients.

Nanometer

Unit used for measurement, equivalent to 10⁻⁹ meters or one-billionth of a meter; abbreviation nm.

Nitrogen fixation

Change of atmospheric nitrogen into nitrogen compounds by certain microorganisms, usually living in close relationship with plant roots. Nitrogen compounds can be used by plants as food. See rhizobia.

Nodule

Swelling or enlargement of roots of plants, predominantly legumes, due to the presence of nitrogen-fixing microorganisms.

Nutraceutical

Food or food product that decreases the risk of disease establishment or progression.

Nucleic acids

Long chains of molecules known as nucleotides, that perform important functions in the cell; two kinds of nucleic acids function in the cell, i.e., DNA and RNA.

Nucleotide

Building blocks of DNA and RNA. Nucleotides are composed of phosphate, sugar and one of four bases, adenine, guanine, cytosine and uracil (RNA) or thymine (DNA). Three bases form a codon, which specifies a particular amino acid; amino acids are strung together to form proteins. Strings of thousands of nucleotides form a DNA or RNA molecule.

Nucleus

Central compartment in cells of higher organisms (eukaryotes); it houses most of the heritable genetic information in a cell in higher organisms.

Oligonucleotide probe

Short piece of DNA that is complementary to a specific piece of DNA in the cell. By marking the probe, it is possible to visualize whether the DNA is present in the genetic material. This forms the basis for DNA diagnostics.

Pathogen

Any organism capable of producing disease.

Peptide

Two or more amino acids, building blocks of proteins, that are chemically linked to each other.

Phage

Virus that infects bacteria, sometimes causing the death of the host organism.

Phenotype

Visible characteristics or traits of an organism, like a plant or an animal.

Phytochemical

Substances found in plants and plant-derived products.

Plasmid

Independent, free-floating circular piece of DNA in a bacterium, capable of making copies of itself in the host cell. Plasmids can be used in recombinant DNA experiments to clone genes from other organisms and make large quantities of their DNA.

Polymerase chain reaction

Commonly used technique that leads to the selective amplification of a nucleotide sequence of interest. The amplified DNA becomes the predominant sequence in the mixture upon PCR amplification. Often used to make nucleotide probes for diagnostics.

Polymorphism

A visible or molecular difference between two contrasting individuals.

Prion

A small protein found in the brain cell membrane. The distorted form of this protein is responsible for the mad cow disease and causes new Creutzfeld-Jakob disease in humans.

Prokaryote/procaryote

Microbial or bacterial cell lacking a true nucleus. Its genetic information is usually in the form of a single long strand of DNA; plasmids exist separate from the primary DNA strand. Contrast with eukaryote.

Promoter

A control region of a gene that determines in which tissue and at what time points a gene product is produced.

Proteomics

The study of proteins.

Protoplast

Cellular material, cytoplasm, mitochondria, nucleus, etc., remaining after the cell wall has been removed.

PST

Porcine somatotropin. Version of growth hormone or somatotropin produced by swine.

Recombinant DNA (rDNA)

As a process: broad range of techniques that involve the manipulation of the genetic material of organisms, also known as genetic engineering or biotechnology. As a product: fragments of DNA from two sources or organisms joined together.

Regeneration

Process of triggering the formation of whole plants from cells removed from the plant and grown in the laboratory under controlled growth conditions. One of the steps involved in the process of demonstrating totipotency.

Restriction enzymes

Class of enzymes that cut DNA at specific locations identified by the sequence of the nucleotides. At the site of the cut other pieces of DNA, sometimes sharing the same recognition sequence, can be inserted next to the original location of the cut.

Rhizobia

Microorganisms or bacteria belonging to the genus, *Rhizobium*, which are commonly involved in fixing nitrogen; normally reside in close relationship (symbiotic) with roots of leguminous plants.

Rhizosphere

Area of soil near the plant roots, normally the location of large populations of microorganisms.

Ribonucleic acid

(Abbr. RNA) Chemical chains made up on the sugar ribose attached to nucleic acid molecules. Different types of RNA exist in cells, some of which serve as the immediate code for proteins, some of which are involved in the physical process of protein synthesis. RNA can also serve instead of DNA as the only genetic information in certain viruses.

Sexual reproduction

Process in which two cells, termed gametes, come together to form one fertilized cell that contains genetic information from both parental cells.

Somaclonal variation

Genetic changes that occur within non-reproductive cells, often during the process of culturing the cells in the laboratory.

Species

Term used to describe the group of like individuals. Classically species were defined as organisms that share certain characteristics.

Somatotropin

Protein hormone secreted by a special organ in mammals, the pituitary gland, and each animal produces its own specific version of the hormone that is active in its own species and in species of lower order but not higher. The hormone directs milk product.

Spore

Particular form of certain microbes that allows the organisms to survive in a dormant stage until conditions improve at which time the spores can germinate and the life cycle resumes.

Sterile

Free of living organisms; the terms usually refers to lack of microorganisms or bacteria. Process of sterilization refers to killing all life forms by heating, chemical treatment or other means.

Strain

Different organism within same species.

Substrate

Material or substance acted upon by an enzyme.

Symbiosis

Two or more dissimilar organisms living together in close association with one another. Includes parasitism, where one of the organisms harms the other(s), mutualism, where association is advantageous to all) and commensalism, where association is advantageous to one organism but doesn't affect other organism(s).

Tissue culture

Process of introducing living tissue into culture in the laboratory where tissues or cells can be grown for extended periods of time.

Totipotency

Capability of certain cells to be cultured in the laboratory and undergo sustained cell divisions. Application of hormonal and other signals triggers the tissue to undergo a programmed, developmental pathway that leads to the reformation of the entire organism.

Transformation

Process of introducing into an organism new genetic information that can be stably maintained.

Transgenic

Organism that contains genetic materials introduced through recombinant DNA techniques. Usually implies that organism contains DNA from another organism.

Transposon

Naturally occurring DNA sequence that is capable of moving its location within the genome; movement is due to the presence of an enzyme that can mediate the movement and which is encoded within the transposon itself. Transposable elements are responsible.

Vaccine

Utilization of a killed or debilitated organism or a part of its contents that is capable of inducing protection against the disease caused by that organism.

Value-added

Trait introduced into an organism/plant that gives that organism added value, like the addition of a valued trait or the capability to produce a new, valued substance, like a pharmaceutical or a biomaterial.

Vector

Agent, such as an insect, virus or plasmid, that is able to mechanically or biologically transfer itself or its contents from one organism to another.

Virulence

Degree or severity of disease-causing potential of an organism.

Virus

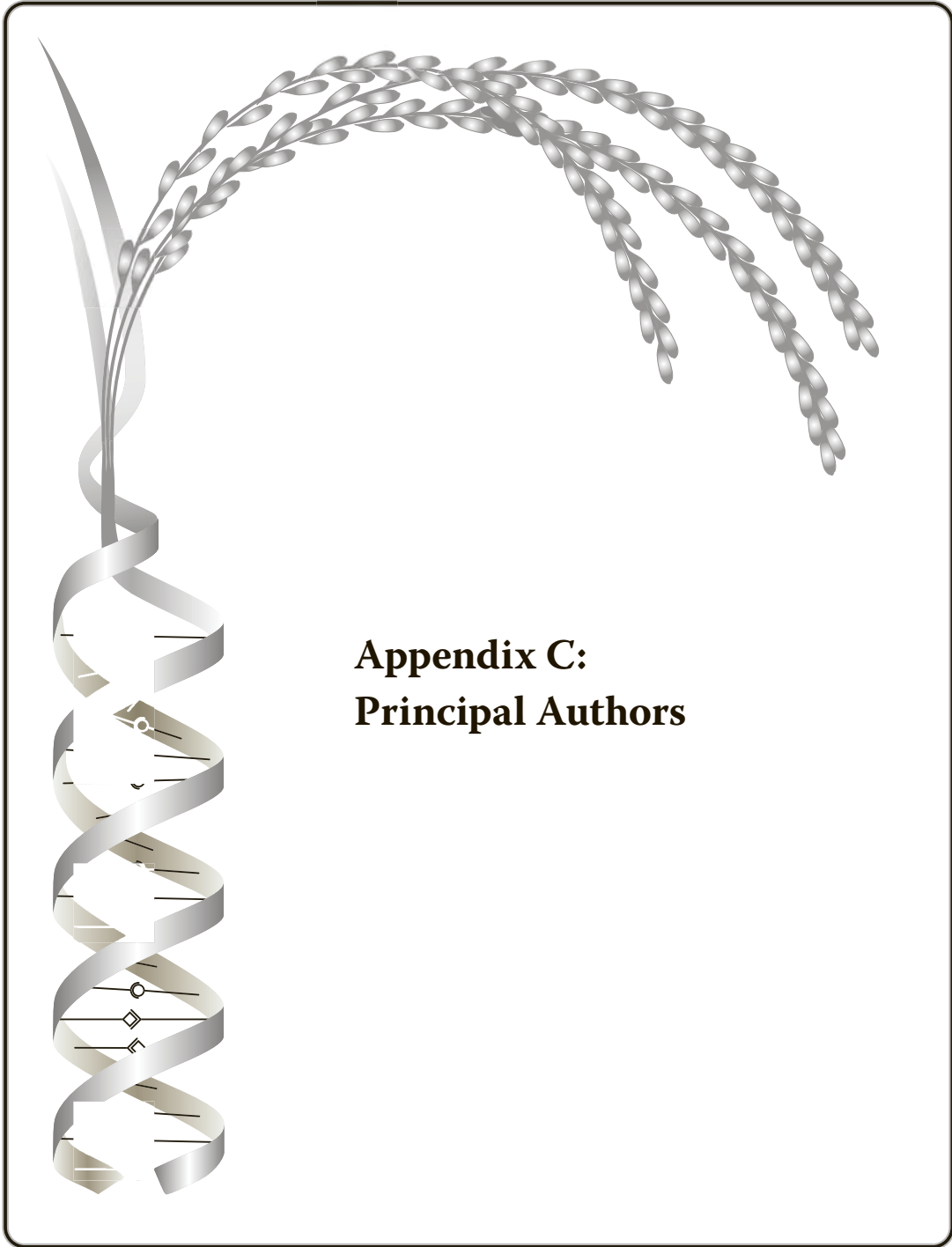
Small genetic element, composed of either DNA or RNA that is protected by a protein coat. Virus is capable of existing either inside a cell (intracellular) or outside a cell (extracellular). Viruses cannot make copies of themselves without invading another cell and using some of its machinery.

Wild-type

Organism as discovered in nature.

Yeast

Kind of fungi or microbe. Yeast are used in bread-, wine- and beer-making to produce fermentation products.



**Appendix C:
Principal Authors**

Appendix C: Principal Authors

George Bruening

Professor in Plant Pathology and Director, Center for Engineering Plants for Resistance Against Pathogens
University of California, Davis

George Bruening received his master's and Ph.D., both in biochemistry, from the University of Wisconsin, Madison. He was a postdoctoral researcher at UC Berkeley and a member of the Biochemistry and Biophysics faculty at UC Davis before transferring to Plant Pathology in 1984. Dr. Bruening's areas of specialization include biochemistry and molecular genetics of plant viruses, plant virus-associated subviral agents and plant pathogenic bacteria, mechanisms of natural and genetically engineered resistance against viruses, and agricultural biotechnology.

Christine M. Bruhn

Consumer Marketing Specialist and Director, Center for Consumer Research
University of California, Davis

Christine M. Bruhn has training in consumer behavior, food science, and consumer economics. She taught food science and consumer courses at the University of California and California State University for over ten years before joining Cooperative Extension in 1986. As a Consumer Food Marketing Specialist, Dr. Bruhn studies consumer attitudes toward food safety and quality and conducts educational programs which inform consumers about new products and new technologies. She is past chair of the Food Science Communicators and the Nutrition Division of the Institute of Food Technologists, has been recognized by the International Association for Food Protection for her work in food safety, and is a Fellow of the Institute of Food Science and Technology of the United Kingdom. Dr. Bruhn served on the Institute Food Technology Expert Report on Biotechnology and Foods. She has authored over one hundred popular and professional papers on consumer attitudes toward food and receives numerous national and international requests to address consumer issues.

Gregory Conko

Policy Analyst and Director of Food Safety Policy
Competitive Enterprise Institute

Gregory Conko is a Policy Analyst and Director of Food Safety Policy with the Competitive Enterprise Institute, a Washington, D.C.-based public interest group dedicated to the principles of free enterprise and limited government, where he specializes in issues of food and pharmaceutical drug safety regulation, and on the general treatment of health risks in public policy. Mr. Conko is particularly interested in the debate over the safety of genetically engineered foods and the application of the Precautionary Principle to domestic and international environmental and safety regulations. He frequently participates in international meetings on food safety and trade as a credentialed Non-Governmental Organization representative.

Mr. Conko is also the Vice President and a member of the Board of Directors of the AgBioWorld Foundation, a nonprofit organization based in Tuskegee, Alabama, which he co-founded. Mr. Conko's writings have appeared in journals, newspapers, and magazines. He holds a Bachelor of Arts degree in Political Science and History from the American University in Washington, D.C.

Norman C. Ellstrand

Professor of Genetics, Department of Botany and Plant Sciences
University of California, Riverside

Norman C. Ellstrand's expertise is in applied plant population genetics with current emphasis on the consequences of gene flow from domesticated plants (including transgenics) to their wild relatives. He has written over a dozen papers on the topic and is currently writing a book as well. He is a member of the National Research Council Subcommittee on Environmental Impacts Associate with Commercialization of Transgenic Crops. Dr. Ellstrand has been a speaker or participant in several government and NGO meetings and workshops concerning transgenics, including a National Research Council planning meeting on Technology and Intellectual Property Challenges Associated with Genetically Modified Seeds. Dr. Ellstrand received a bachelor's degree from the University of Illinois and a Ph.D. in Biology from the University of Texas. His honors include a Fulbright Fellowship to Sweden.

Subray Hegde

Postgraduate Research Geneticist, Department of Botany and Plant Sciences
University of California, Riverside

Subray Hegde received his Ph.D. in Genetics and Plant Breeding from the University of Agricultural Sciences, Bangalore, India. He was holding an Assistant professor position in the same institution before coming to the United States. Dr. Hegde's research work combines both theoretical and applied tools of genetics and evolutionary biology. His earlier work includes economic yield improvement in cereals and legumes using index selection and multiple-trait selection. He worked extensively on plant reproductive and dispersal evolution of tropical plant species and on population genetics of wild and weedy relatives of bread wheat. Dr. Hegde's current research interests include ecological genetics of invasive plant species and quantification of gene flow between crop cultivars and between crops and wild relatives.

Dave Luscher

Senior Agricultural Biologist
California Department of Food and Agriculture

Dave Luscher is employed as a Senior Agricultural Biologist in the California Department of Food and Agriculture (CDFA) Office of Pesticide Consultation and Analysis since 1996. From 1990 through 1996, he held the position of Associate Agricultural Biologist with the CDFA Pest Exclusion Branch. From 1985 through 1990, he was a Pesticide Registration Specialist with the CDFA Pesticide Registration Branch. He received a B.S. in Plant Science from the University of California at Davis.

Henry I. Miller
Research Fellow
Hoover Institution

Henry I. Miller, M.S., M.D., is a research fellow at the Hoover Institution. His research focuses on science and technology and their regulation, especially pharmaceutical development and regulation; and federal, domestic, and international oversight of the products of genetic engineering. Author of "Policy Controversy in Biotechnology: An Insiders View."

Dr. Miller joined the Food and Drug Administration in 1979 and served in a number of posts involved with the new biotechnology, including special assistant to the FDA commissioner, with responsibility for biotechnology issues; from 1989 to 1994, he was the founding director of the FDA's Office of Biotechnology. During his government service, Dr. Miller participated frequently on various expert and policy panels, as a representative of the FDA or the U.S. government. While a government official, Dr. Miller was the recipient of numerous awards and citations.

Dr. Miller's primary contributions have been in four areas: as a federal official, crafting and implementing science-based regulation, and explaining these policies to regulated industry, the scientific community, and the public; as a member of international panels and experts groups, moving consensus toward the scientific view of risk assessment and management; making science and technology and their regulation more widely understood, via articles in newspapers and magazines; and performing research on and analyses of various issues related to science and technology, including the description of models for regulatory reform.

Tamara Schiopu
MBA Candidate
University of California, Riverside

Tamara Schiopu received a Diploma of Excellency from the Academy of Public Administration, Government of Moldova and is currently an MBA candidate, graduating in June 2002, from the A. Gary Anderson Graduate School of Management at the University of California, Riverside. She is currently a teaching assistant and research assistant at UCR. Her past experience includes working as a summer intern for the Tolhust Organic Produce company in the UK, acting as a liaison officer for the UC Division of Natural Resources and Agriculture in Moldova, and working as a project assistant, project coordinator and project manager for the Plunkett Foundation, UK in European Union Technical Assistance for Commonwealth Independent States. Tamara has knowledge of five languages and is focusing her research interests in the field of corporate environmental management at UCR.

John Steggall
Senior Environmental Research Scientist
California Department of Food and Agriculture

John Steggall works for the California Department of Food and Agriculture where he analyzes economic impacts of pesticide regulatory decisions. This work is done in conjunction with agricultural economists at UC Berkeley and CDFA, as well as UC Cooperative Extension faculty. Dr. Steggall has also worked at the California EPA's Department of Pesticide Regulation where he analyzed pesticide alternatives and trends in pest management. He has degrees from Colorado College, University of Michigan, and a Ph.D. in entomology from UC Berkeley.

Seymour D. Van Gundy

Professor and Dean Emeritus, College of Natural and Agricultural Sciences
University of California, Riverside

Seymour Van Gundy served as dean of the UCR College of Natural and Agricultural Sciences from 1988 to 1993. Dr. Van Gundy, Professor Emeritus of Nematology and Plant Pathology, was elected an Honorary Member of the Society of Nematologists, the highest honor bestowed by the organization for meritorious and superlative contributions to the field. At UCR, Dr. Van Gundy has served as Chair of the Department of Nematology, Associate Dean for Graduate Research, Assistant Vice Chancellor for Research and Dean of the College of Natural and Agricultural Sciences. He has served as editor in chief of the Journal of Nematology and vice president and president of the Society of Nematologists. He is a fellow of the American Association for the Advancement of Science, fellow of the Society of Nematologists and fellow of the American Phytopathological Society. He has served as an Agricultural reviewer/consultant to NAS, NSF, USDA, USAID, US State Department, WASC, CCST and University Extension.

He has been appointed by California Gov. Gray Davis to the Santa Ana Regional Water Quality Control Board, Santa Ana Region. He also serves on State Boards for CDFR-Citrus Research Board, and State Parks-California Citrus State Historical Park Board.

John Vanderveen

Emeritus Scientist, Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration

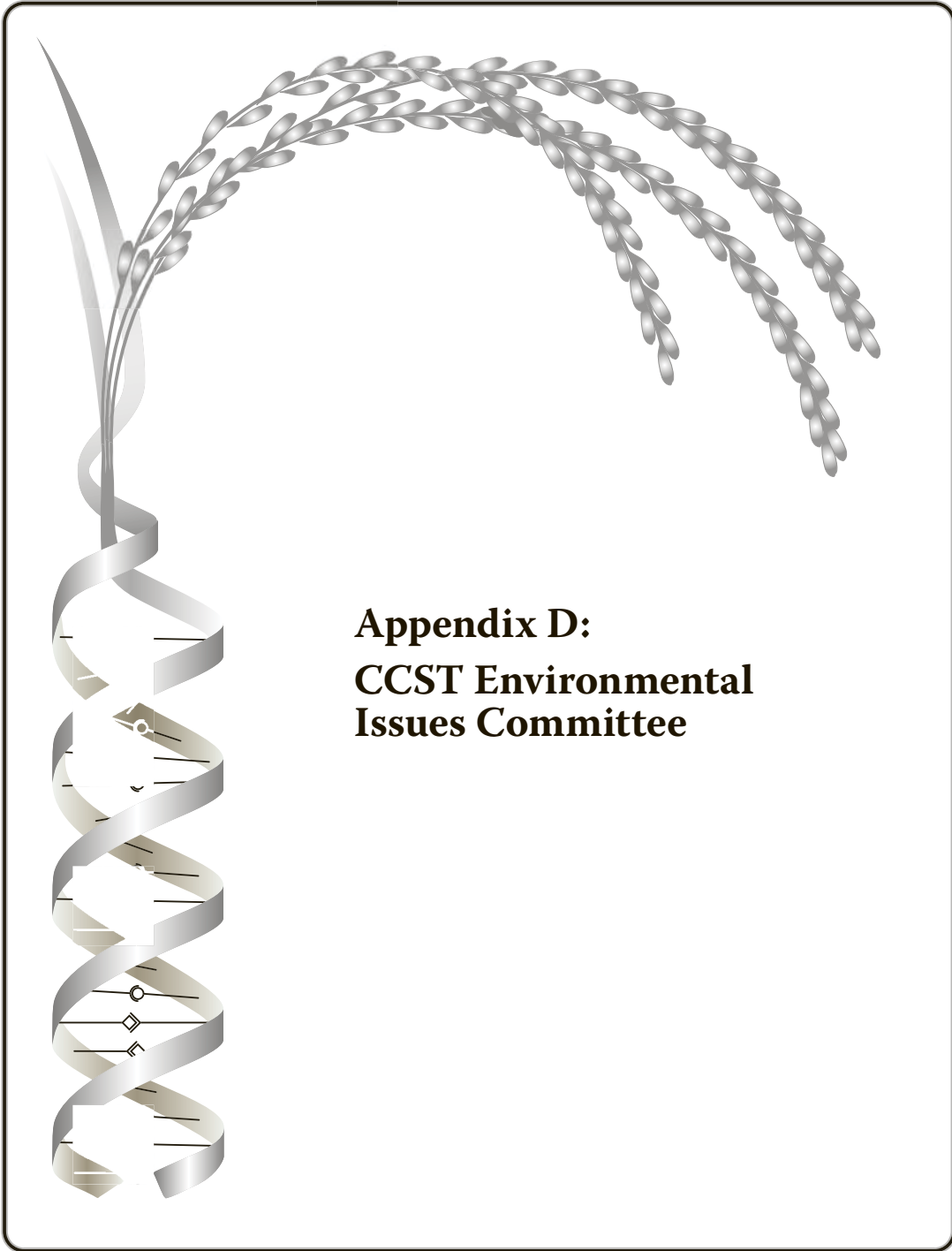
John Vanderveen is an Emeritus Scientist of the Center for Food Safety and Applied Nutrition of the U.S. Food and Drug Administration (FDA). Before he retired from the FDA he served as the director of the FDA's Office of Plant and Dairy Foods and Beverages. In that capacity he was responsible for the regulation and policy development of all foods and beverages derived from plants, milk and game animals except infant formulas, medical foods and dietary supplements. Also in this capacity he represented the Agency on several Codex committees and other international committees. Prior to that position he was the director of the Center's Division of Nutrition and was responsible for the Agency's nutrition research and development of nutrition policy. He also served in various capacities at the USAF School of Aerospace Medicine at Brooks Air Force Base, Texas where he was responsible for the USAF research and development program in the areas of foods and nutrition. He retired with more than 38 years of government service. Since retirement he has served as the Chair of the Committee on Military Nutrition Research of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. During his career he became a professional member of a number of scientific societies including the American Society for Nutritional Sciences, the American Society for Clinical Nutrition, the American Chemical Society and the Institutes of Food Technologists. He received a number of awards for service from the FDA and the Air Force. Dr. Vanderveen holds a B.S. in agriculture from Rutgers University in New Jersey and a Ph.D. in chemistry from the University of New Hampshire.

Brian D. Wright

Professor Agricultural and Resource Economics and Co-Director of Environmental Sciences
University of California, Berkeley

Brian Wright's interest in agricultural economics dates from his early experiences on his family's sheep station in the Riverina district of New South Wales, Australia. He received a Bachelor of Agricultural Economics (First Class Honors) from the University of New England, Armidale, and was awarded one of the two Frank Knox Fellowships given annually to Australian students by Harvard University, where he received an A.M. and Ph.D. in Economics. He then taught at Yale University and is now Professor of Agricultural and Resource Economics at the University of California, Berkeley, where he is also Co-Director of Environmental Science.

Dr. Wright's current research interests include dynamic analysis of research incentives and their effects on industrial structure, the theory of commodity price behavior and speculation, and the economics of conservation of biodiversity resources. Recently he has served as the economist member of the Subcommittee on Proprietary Science and Technology of the Consultative Group on International Agricultural Research (CGIAR), and he presented a paper on "Intellectual Property Rights in Agricultural Biotechnology" at the recent Washington D.C. meeting of the Committee on Science, Technology, and Economic Policy (STEP) of the National Research Council. Dr. Wright has also served as an expert witness regarding patent licensing and agricultural biotechnology as well as consulted for the United States Department of Justice.



**Appendix D:
CCST Environmental
Issues Committee**

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COMMITTEE CHARGE

Identify, evaluate, and recommend to the Council programs, activities, and actions (i.e.) to enhance the use and value of science and technology for ensuring environmental quality and sustainability in California and to address environmental issues relevant to California where the science and technology is a significant component in the issues.

Analyze, evaluate, and advise the Council on requests to the Council for assistance regarding environmental matters.

Ensure that environmental matters are continuously relevant to considerations by the Council in its varied programs, activities, and actions.

Henry E. Riggs, Chair

Henry E. Riggs began his career in 1957 as a process engineer at the Ampex Corporation. After 3 years at the Stanford Research Institute, Mr. Riggs joined Icore Industries, where he completed his tenure as President and Chief Executive Officer. Mr. Riggs subsequently served for five years as the Chief Financial Officer of Measurex Corp. From 1961 to 1966, Mr. Riggs taught economics at Foothill College, and between 1967 and 1974 was a lecturer at Stanford University. In 1974 he joined Stanford full time, was appointed a tenured full professor in 1980, and was named the Thomas W. and Joan B. Ford Professor of Engineering in 1985. From 1978 to 1982 he served as Chairman of the Department of Industrial Engineering and Engineering Management, and from 1983 to 1988 as the University's Vice President for Development.

In 1988, Mr. Riggs became the President of Harvey Mudd College, the undergraduate college of science and engineering at Claremont. He served as President until early 1997, when he resigned to devote himself full-time to creating the Keck Graduate Institute of Applied Life Sciences.

Mr. Riggs holds an M.B.A. (with high distinction) from Harvard University, and a B. S. (with distinction) in Industrial Engineering from Stanford University. Mr. Riggs' areas of academic specialization include management of technology, technical strategy, new venture management, financial analysis and control.

Robert P. Caren

Chris Caren is the former Corporate VP of Science and Engineering at Lockheed Corporation, where his career spanned over 30 years. Dr. Caren is a fellow of the American Association for the Advancement of Science, the American Institute of Aeronautics and Astronautics, the American Astronautical Society, the Institute for the Advancement of Engineering and the Society of Automotive Engineering. He is also a member of the National Academy of Engineering. He is a founder and member of the Board of Directors of Litex Inc. a company involved in automotive emission reduction systems. He is chairman of Hawkeye Enterprises a company involved in the upgrade of subquality natural gas. He is also a member of the Board of Directors of Superconductor Technologies Inc

Jerry D. Caulder

Jerry D. Caulder is the founder of Akkadix Corporation, an agricultural biotechnology company that develops proprietary technology in the crop protection and seed industries. Dr. Caulder is also the Executive Chairman of Myelos Co., a neuro-science company. Caulder is the former Chairman, President and Chief Executive Officer of Mycogen Corporation, and former chairman of the Industrial Biotechnology Association, a predecessor to BIO. He has served on and chaired several committees of the U.S. Office of Technology Assessment, given expert testimony before both houses of Congress, and advised foreign governments on agriculture and biotechnology. He is a member of the Advisory Council on Small Business and Agriculture of the Federal Reserve Board of San Francisco.

Susan Hackwood

Susan Hackwood is currently Executive Director of the California Council on Science and Technology and Professor of Electrical Engineering at the University of California, Riverside.

Dr. Hackwood received a Ph.D. in solid state ionics in 1979 from DeMontfort University, UK. Before joining academia, she was Department Head of Device Robotics Technology Research at AT&T Bell Labs. In 1984 she joined the University of California, Santa Barbara as Professor of Electrical and Computer Engineering and was founder and Director of the National Science Foundation Engineering Research Center for Robotic Systems in Microelectronics.

In 1990, Dr. Hackwood became the founding Dean of the Bourns College of Engineering at the University of California, Riverside. Dr. Hackwood's current research interests include science and technology policy, distributed asynchronous signal processing and cellular robot systems. She has published over 140 technical publications and holds 7 patents.

Charles F. Kennel

Charles F. Kennel is author or co-author of over 250 experimental and theoretical publications in his field. He has been a Fulbright and Guggenheim scholar, and a Fairchild Professor at Caltech. He is a fellow of the American Geophysical Union, the American Physical Society, and the American Association for the Advancement of Science, and a member of the International Academy of Astronautics; the National Academy of Sciences and the American Academy of Arts and Sciences. His many awards include the NASA Distinguished Service Medal; the James Clark Maxwell Prize, American Physical Society; and the Aurelio Peccei Prize for Environmental Science. He serves on advisory panels and boards including the NASA Advisory Council.

Elisabeth Paté-Cornell

Elisabeth Paté-Cornell is the Burt and Deedee McMurtry Professor in the School of Engineering and professor and chair of the department of Management Science and Engineering at Stanford University. Her research, in recent years has focused on the extension of probabilistic risk analysis models to include human and organizational factors, with applications, for example, to the maintenance of the tiles of the space shuttle, the management of offshore oil platforms, and anesthesia in operating rooms. She is currently involved in the development of decision support systems for the management of engineering programs of dependent projects such as unmanned space missions under tight constraints of time and budget.

Her undergraduate degree was in mathematics and physics. She received her graduate Engineer Degree in Computer Science in 1971 from the Institut Polytechnique of Grenoble, France, a Master's degree in Operations Research in 1972, and a PhD in Engineering-Economic Systems in 1978, both from

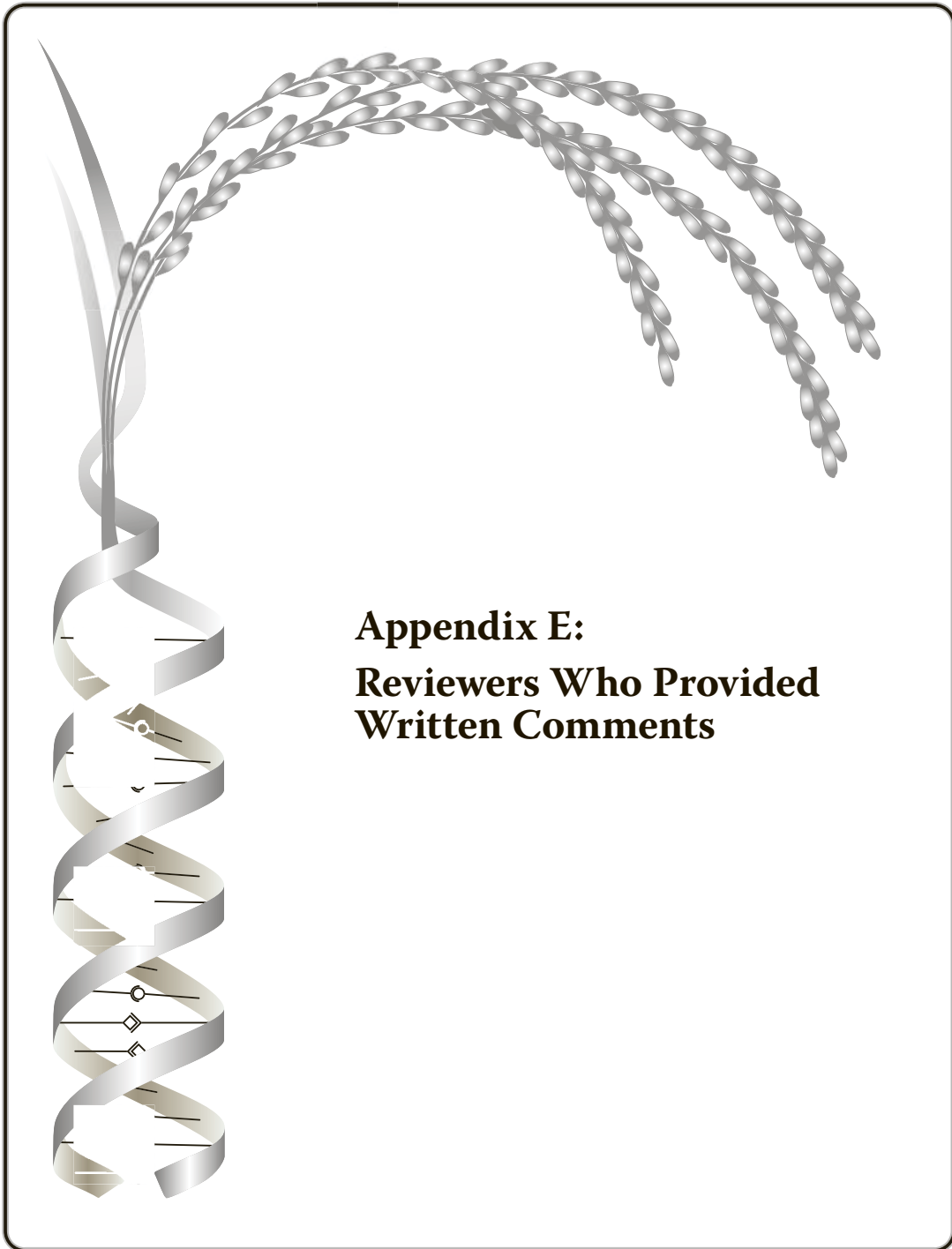
Stanford University. She taught at MIT in the department of Civil Engineering (78-81) and at Stanford in the department of Industrial Engineering and Engineering Management (81-99) which she chaired from 1997 to 1999. She is currently the chair of the newly formed department of Management Science and Engineering resulting from the fusion in January 2000 of the former departments of Industrial Engineering and Engineering Management, and of Engineering-Economic Systems and Operations Research.

C. Bruce Tarter

C. Bruce Tarter is the eighth director of the Lawrence Livermore National Laboratory. His career began in 1967 as a member of the Theoretical Physics Division, and he has served in various technical leadership assignments at the Laboratory in weapons physics, geosciences research, and space programs including strategic defense projects. Dr. Tarter has served on numerous research and institutional management committees within and outside the Laboratory, has been a lecturer and graduate student advisor at the Department of Applied Sciences of the University of California, Davis/Livermore, and is an Adjunct Professor, Department of Applied Science, University of California, Davis. Memberships include the American Physical Society, American Astronomical Society, International Astronomical Union, and the American Association for the Advancement of Science. He received the Roosevelt Gold Medal Award for Science and is a Fellow of the American Physical Society.

Daniel Vapnek

Daniel Vapnek, currently an advisor to several high technology companies, served as Senior Vice President of Research of Amgen from 1981 to 1997, having previously led Amgen's research programs as Vice President and Director of Research. Prior to joining Amgen in 1981, Dr. Vapnek held positions as Assistant Professor, Associate Professor and Professor of Molecular and Population Genetics at the University of Georgia during a period of nine years. Dr. Vapnek received his undergraduate training and, in 1968, obtained his Ph. D. in Microbiology from the University of Miami. He moved to Yale University's School of Medicine as a US Public Health Service Post-Doctoral Fellow and served there as a Research Associate before accepting his appointment at the University of Georgia in 1972.



**Appendix E:
Reviewers Who Provided
Written Comments**

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Peer Review Process

The California Council on Science and Technology has the highest principles in providing independent, objective and respected quality work. The Council is in itself a review process in that all work that bears the Council's name is reviewed by council members, fellows, and outside experts. The Council seeks guidance and approval of outside experts for peer review, not with the outcome, but with the process used. This results in a protocol that ensures the issue is well addressed, the response is targeted and that the results are clear and sound.

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Henry Chin*, Vice President, National Food Processors Association

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James Cook, Endowed Chair in Wheat Research, Washington State University

Cynthia Cory*, Director of Environmental Affairs, California Farm Bureau Federation

Jason Dietz, Consumer Safety Officer, Division of Product Policy, Office of Premarket Approval, The Center for Food Safety and Applied Nutrition of the U.S. Food and Drug Administration

Norman Ellstrand*, Professor of Genetics, University of California, Riverside

Anthony Hall, Professor of Plant Physiology and Crop Ecologist, University of California, Riverside

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Cynthia Wagner Weick*, Associate Professor, Management, University of the Pacific

H. Michael Wehr, Special Assistant to the Director, Office of Constituent Services, The Center for Food Safety and Applied Nutrition of the U.S. Food and Drug Administration

Carl Winter, Director, FoodSafe Program, University of California, Davis

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Christine Bruhn, Director, Center for Consumer Research, University of California, Davis

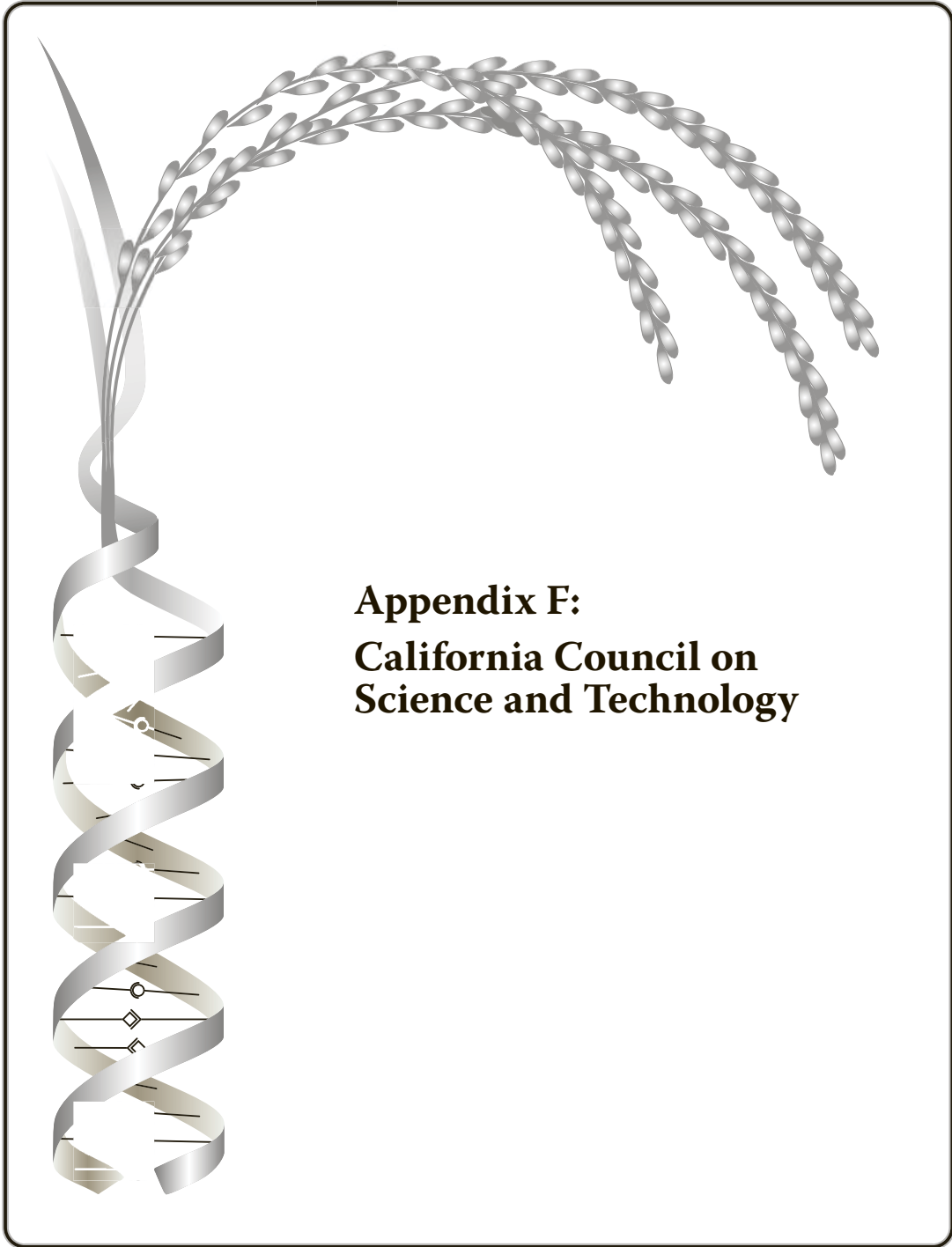
Norman C. Ellstrand, Professor of Genetics, University of California, Riverside

Henry I. Miller, Senior Fellow, Hoover Institute

Seymour Van Gundy, Dean Emeritus, College of Natural and Agricultural Sciences, University of California, Riverside

John Vanderveen, Emeritus Scientist, Center for Food Safety and Applied Nutrition

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**Appendix F:
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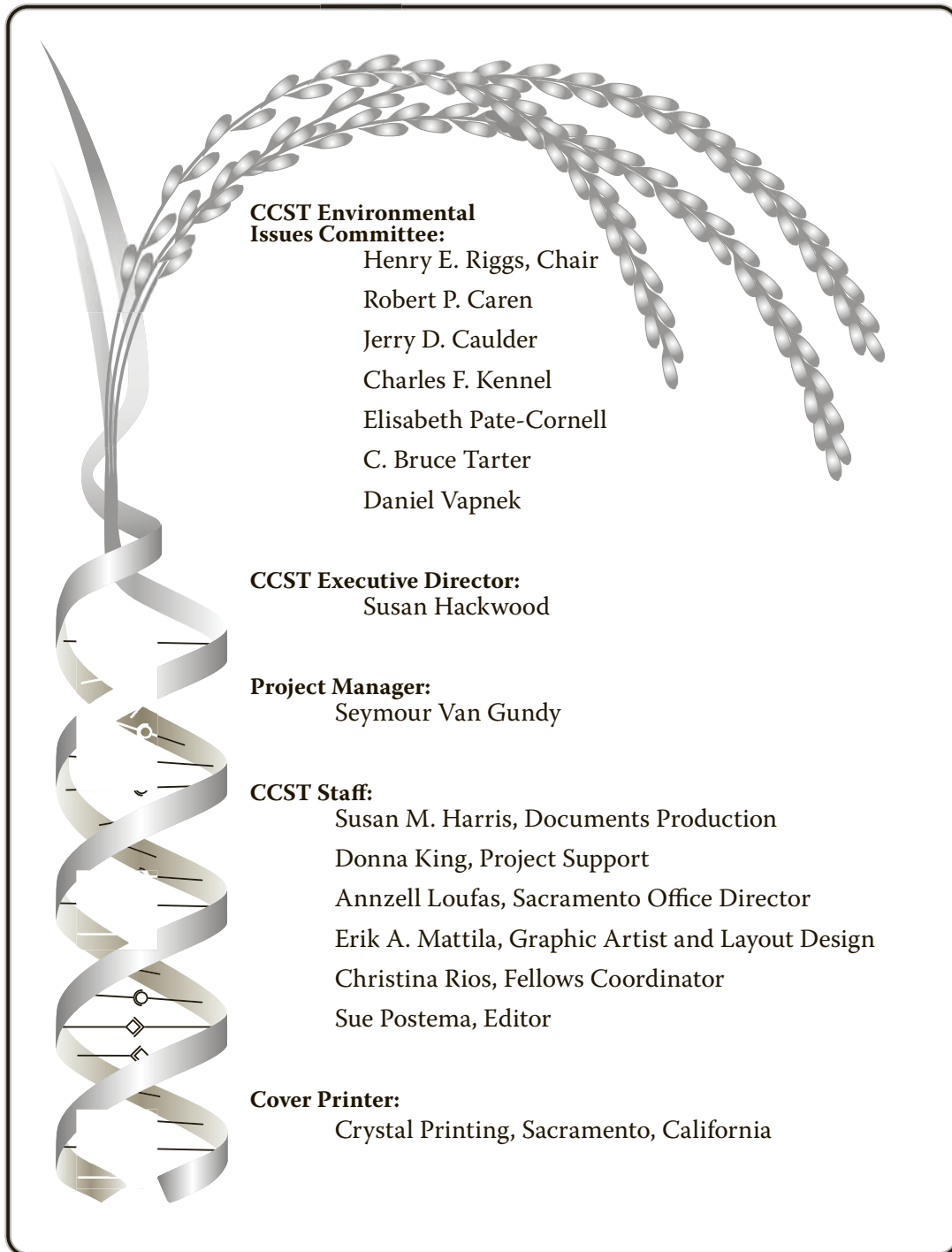
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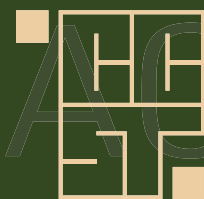
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